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BRAIN

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THE INSULA

FURTHER OBSERVATIONS ON ITS FUNCTION[1]

BY

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THE function of the hidden cortex of the Island of Reil has long been a subject for speculation. Early anatomists and physiologists regarded it diversely as a centre for speech (Rose, 1928) or for taste (von Bechterew, 1899). Direct observations on the human insula were impossible until recent years when it was recognized that focal epilepsy, arising in the temporal lobe, could be treated with a reasonable hope of success by partial temporal lobectomy.

In preparation for this study of the insula, one of us (M. E. F., Jr.) has applied the technique of gastromotor recording, while craniotomies were in progress under local anæsthesia. He found, as will be described below, that definite effects upon gastric motility and tone were produced by stimulation of the insula and by its removal but not by similar procedures carried out in other areas of cerebral cortex.

It is obvious that such operations must be planned with no purpose in mind except the cure and the comfort of the patient. Opportunity to make scientific observations must wait on the chance of therapeutic procedures. The clinical investigator must possess his mind with patience. He must be prepared to make records when he can, but his reward may well be great, for a man can give so much more valuable information than an experimental animal can. However, all too often when the golden opportunity presents itself, we lack the wit to ask the right question!

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It was the early experience of one of us (W. P.) that focal epileptic seizures arising in the insula produced abdominal sensations and gastro-intestinal movement and this was substantiated, from time to time, by electrical stimulation under local anæsthesia (Penfield and Rasmussen, 1950; Penfield and Kristiansen, 1951; Penfield and Jasper, 1954). But other responses were often obtained as well, and doubt arose as to the validity of this conclusion.

Because of these findings our associate, Professor B. P. Babkin, made a series of studies of this problem in laboratory mammals with Kite (1949), Speakman (1950) and Van Buren (1951). They concluded that there was, in dogs, a vagal motor "centre" in the insular-orbital region corresponding to the vagal sensory representation on the orbital surface. Considering the homology between the brain of dog and man, they concluded that there was in their experiments substantial support for the control of gastric motility which had been suggested for man.

Babkin pointed out that the whole "feeding pattern" formed a downward extension of the motor representation in the dog's cortex. Below the motor representation (hind-limb, fore-limb and jaw), the "feeding pattern" appeared on the anterior composite gyrus as follows: mastication, inhibition of respiration, salivation, swallowing, œsophageal contraction and inhibition of the pyloric antrum of the stomach.

Literature

Stimulation of the insular cortex of the monkey is reported to have produced respiratory, somatomotor and circulatory effects (Hoffman, and Rasmussen, 1953; Kaada, 1951; Kaada, Pribram and Epstein, 1949; Sugar, Chusid and French, 1948; Wall and Davis, 1951).

Only inhibition or arrest of respiratory movements was obtained from stimulation of the anterior insula, especially the limen insula. Paradoxical cardiovascular effects are produced by stimulation of this same area. A sudden fall in blood pressure was the usual response, while a slow elevation of blood pressure was obtained from other points.

Gastromotor responses were also variable. A decrease in amplitude or complete inhibition of gastric activity might be obtained, or stimulation might produce augmentation of both rate and amplitude. All of these responses have been shown to be cortical and discretely focal by means of isolation, procainization, and undercutting of the responsive areas.

Hoffman and Rasmussen (1953) and Kaada (1951) have demonstrated that these cardiovascular and gastric motor responses obtained by stimulation of the cortex may be abolished by section of the vagus nerve.

There is no clue as to their route of travel from cortex to medulla nor as to the collaboration of other cortical or subcortical structures in these responses.

In addition to these primarily autonomic effects somatomotor inhibition was obtained by Kaada (1951) from the anterior insula, and patterned motor movements were obtained by Sugar *et al.* (1948) from the posterior insular cortex.

Results similar to the preceding were reported from stimulation of essentially comparable cortical areas in carnivores (Babkin and Speakman, 1950; Babkin and Van Buren, 1951; Bailey and Sweet, 1940; Delgado and Livingston, 1948; Eliason, 1952; Kaada, 1951; Kite, 1949; Speakman and Babkin, 1949). As a result of these experiments, the anterior insula has been linked with the inferior sensorimotor area as a centre for the "feeding pattern" (Babkin and Van Buren, 1951) or with the posterior orbital area (Wall and Davis, 1951) and temporal pole (Kaada, 1951) as a cortical centre for regulation of autonomic activities.

In one reported instance bilateral ablation of the insular cortex in monkeys was followed by no observed deficit, but impairment of the sense of taste was obtained after bilateral combined lesions of the anterior insula, operculum, and superior temporal plane (Bagshaw and Pribram, 1953).

Material

(1) This report is based on the examination of the records of all cases in the Montreal Neurological Institute, from 1945 to 1953 inclusive, in which positive results of insular stimulation were recorded during surgery for focal epilepsy.[1] In the interest of completeness, previously reported cases (Penfield and Kristiansen, 1951; Penfield and Rasmussen, 1950; Penfield and Jasper, 1954) have been included.

(2) In addition special recordings have been made of the results of all operative stimulations during a recent period of six months, as will be described.

Method

Stimulation of the exposed insular cortex and recording of results

[1]Some of these patients were operated upon by our associates who studied this problem with us during these years, Theodore Rasmussen, Keasley Welch, Harry Steelman, Kristian Kristiansen, Lamar Roberts, Maitland Baldwin, William Feindel. Special studies were carried out by Gabriel Mazars, Birger Kaada and E. A. Pask during our operations.

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were carried out during the course of craniotomy under local anæsthesia.[1] Special methods for recording were set up in the operating room with consultation from Herbert Jasper, H. S. Morton and André Pasquet.

Several stimulators were employed in succession including the Thyratron, the Rahm stimulator and, more recently, a square wave generator. A current of 30 to 60 cycles per second was used, of a voltage rarely greater than twice that required for threshold response in the Rolandic motor and sensory strip. Most of the results described in this paper were obtained with the use of the square wave generator which is in use at the present time. With this generator a standard frequency of 60 cycles and pulse duration of 2 milliseconds were used routinely, with potentials ranging from ½ to 5 volts. Duration of the stimulation varied from 1 to 30 seconds.

Thoracic and abdominal respiration and blood pressure changes were recorded. Electrocardiograms and gastrograms were also made on a much-modified Gilson Medical Electronics electroencephalograph, re-christened an "Autonomograph." These special recording techniques were installed during operations.

Loops of small flexible rubber tubing, filled with saline, were strapped to the chest and abdomen and connected through a Wheatstone bridge for the recording of respiration. Continuous blood pressure records were obtained by means of an intra-arterial catheter connected to a Lilly manometer. Gastric tone and motility were recorded by means of an inflated intra-gastric balloon, also connected to a Lilly manometer.

In the most recent experiments, gastric function was recorded by means of an electrogastrograph (Martin and Morton, 1952). Gastric potentials were obtained from a swallowed silver-silver chloride electrode in saline contact with the gastric mucosa, amplified by a vacuum tube D.C. amplifier, and recorded on an Esterline-Angus recording milliammeter.

Electrode position was checked by X-ray. Food had been withheld from these patients for a twelve-hour period as a routine preoperative measure and oral nutrient fluid was given four hours before operation.

Clinical Correlation

The clinical picture presented by patients with lesions involving the insular and peri-insular regions has previously been presented in some detail (Penfield and Jasper, 1954) and will not be discussed here except in so far as it applies to the experimental data.

All of the patients in this series were seeking relief from focal epileptic seizures. In many cases the pattern of attack was complex and presented elements referable to various areas in the temporal and Sylvian regions.

Nine of the cases included in this study showed gross anatomical abnormalities of the insular cortex as exposed at operation. When it was the site of epileptogenic discharges, the insular cortex or a portion thereof was typically tough, yellow, and atrophic. In these (and

[1]The handling of these patients during radical operation for treatment of focal epilepsy at the Montreal Neurological Institute is described elsewhere (Penfield and Jasper, 1954).

another 2 patients exhibiting no gross insular abnormality) abnormal electrical activity of the insular cortex was detected by electrocorticography. Spikes and sharp waves were the typical electrographic disturbances and were often found to be very sharply localized to the insular surface.

No neurological deficit attributed to lesions of (or removal of) the Island of Reil could be found in any of these patients. Neurological defects found in this group were few and mild and, in every case, could be attributed to larger lesions of the surrounding cortical areas.

Observations

Positive responses were obtained from the stimulation of a total of 82 separate points on the insular cortex of 36 patients. The majority of these responses can be divided into two distinct groups: gastric sensory or motor phenomena were the result of 32 stimulations; and somatic sensations were the result of 30. Varied sensory and motor phenomena, not falling clearly in one of these two main groups, were obtained on 20 occasions and will be dealt with separately.

It should be noted that the distribution of stimulus points over the surface of the insular cortex (*see* diagrams) was influenced by the fact that the inferior portion of the insula was easily accessible after removal of the anterior temporal lobe, but the fronto-parietal opercula could not ordinarily be elevated for fear of producing severe neurological damage. Consequently, it was only in an occasional case, in which removal of these opercula proved necessary, that it was possible to explore the upper and anterior limits of the island. Such cases are those of B. McK. and G. B. described below.

(1) *Character of visceral sensory phenomena.*—When stimulation of the insula produced an abdominal sensation, it was reported by the patient variously as follows: "something funny" referred to the abdomen, also "gurgling," "rolling," "pain," "nausea," "scratching" or simply as "sensation." The sensation was most often felt in the region of the xiphoid process, the epigastrium, or the umbilicus. Also, there might be associated phenomena such as respiratory inhibition, chewing, swallowing and salivation. Occasionally there was coincidental sensation in the throat or indescribable sensations of taste or smell.

(2) *Recording of visceral motor phenomena.*—In some instances there was associated objective evidence of intra-abdominal motor activity such as borborygmus, belching, or vomiting. In 4 cases an objective record of alteration in gastric motility and tone was made.

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When no stimulation was being carried out, the inflated intragastric balloon or the electrogastrograph usually showed normal gastric contractions at the rate of 2 to 3 per minute or at the rate of 9 to 12 per minute. At other times the stomach was quiet or there were spontaneous slow variations of gastric tone. This was in conformity with the observations of Martin and Morton (1952) and Morton (1954) with these methods of recording.

We observed that excessive pain, resulting from traction on subdural veins, strongly inhibited normal gastric motility. This pain was completely relieved by direct injection of the gasserian ganglion, and with this relief such inhibitory influences disappeared. Pentothal, which was administered only rarely, also inhibited gastric activity.

When satisfactory recording was carried out by balloon and electrogastrograph, insular stimulation produced results which varied from complete inhibition of gastic motility to the production of violent activity with marked increase in tone. There were well-defined and indubitable reactions in 4 out of 6 such patients.

These changes may be described as follows : initiation of 3 or 12 per minute activity superimposed on a previous resting record, change of rate

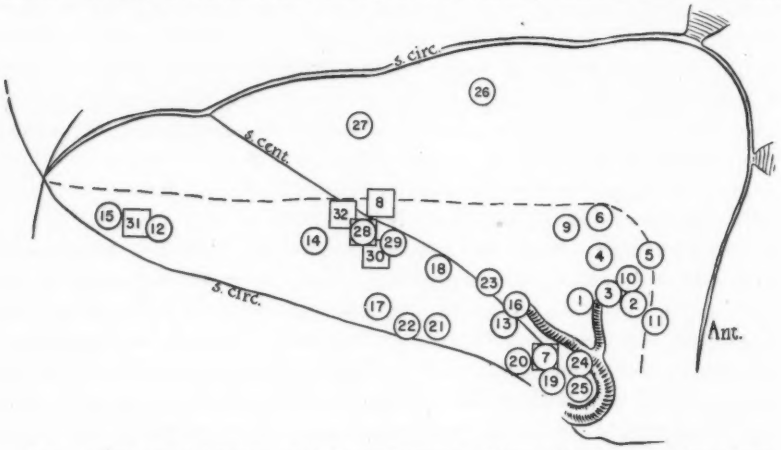

FIG. 1.—Visceral Sensory and Motor Response Chart—Insula. Positive stimulation points from R. and L. sides have been summarized on this diagrammatic representation of the right insula. The area above and to the right of the broken line is covered by the parietal and frontal opercula during most operations. The area below is exposed regularly when the temporal operculum is removed in routine partial temporal lobectomy for temporal lobe seizures. Circles represent visceral sensory responses, and squares pyloric motor responses. When recorded motor responses were accompanied by visceral sensation the circle is squared. The numbers correspond with detailed descriptions of the responses given in the text.

of gastric contraction from 3 to 12 per minute, and changes in amplitude of contractions observed as a result of insular stimulation. Both increase and decrease of tone were observed independently of, or synchronously with, changes in rate or amplitude of gastric contractions.

There was so much variation in the type of gastric sensation produced by stimulation and such a complexity of associated motor and sensory phenomena that it seems wise to report them in detail. The following sensations are reported in the patient's own words when possible. Responses are grouped under the individual's initials, and the numbers refer to the position of the stimulus on the cortex of the insula, as shown in fig. 1 Visceral sensory responses are indicated by circles in this figure. Visceral motor phenomena are indicated by squares. When visceral sensations accompanied some motor manifestation, the circle is squared. When the response is reported as part of the patient's aura, a brief summary of the relevant ictal manifestations follows:

(3) *Case records of visceral phenomena.*—The results of stimulation of the insula were as follows (fig. 1):

S. M.	1	Rising gastric sensation and salivation beginning in epigastrium and moving toward throat (aura).
J. O'L.	2	Rolling in epigastrium and taste (aura).
N. K.	3	Like an attack. A pang of fear in the chest (aura).
	3	Repeated. Feeling as if she were going to be sick.
	3	Further stimulation of this point repeatedly reproduced the aura.
A. Ki.	4	Swallowing, "I smelt something funny," felt something in stomach (left leg numb, "Felt like I had to move it").
	5	Something funny in mouth and stomach. Said he swallowed to get rid of bad taste in his mouth.
	5	Repeated. "My stomach is upset and I smell something like medicine, a sickly smell."
	6	Sensation in abdomen.
	7	"A sickish taste in my throat coming up into my mouth" (recorded inhibition of gastric motility and tone).
	8	Sudden flow of fluid from stomach through tube.
	8	Repeated. Recorded inhibition of gastric motility and tone. (Aura, feeling in stomach moving to throat where it was a taste.)
J. G.	9	"Almost sick to my stomach."
N. H.	10	Depression of respiration and abdominal sensation.
P. M.	11	"My stomach went up and down like when you vomit."
J. McC.	12	"I feel like I cannot swallow."
	12	Repeated. "I feel like I want to vomit."
Y. S.	13	Sensation in stomach.
	14	Sensation in abdomen.
	15	Sensation in abdomen like aura.
	16	"Scratches in stomach."
	17	Sensation in abdomen.
	18	Points to stomach, "Yes." Like an attack? "Yes."

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	19	Like before an attack. Aura. Epigastric burning.
J. C.	20	Attack going on to nausea.
	21	Feeling about umbilicus.
	22	"This is it." "Going to bring up some gas." "Scared to death."
	22	Repeated. Nausea and "far away" feeling, "scared." (Aura. Peri-umbilical pain.)
G. B.	23	Sensation at costal margin, left.
	24	Same.
	25	Bad sensation in stomach (pointed to left costal margin).
	26	Sensation in epigastrium.
	27	Disagreeable taste and gastric sensation.
	27	Repeated twice. Same.
D. C.	28	Sinking feeling in abdomen. (Recorded initiation of 10 per minute gastric activity.)
	28	Repeated. Same.
	28	Repeated. Sinking feeling in abdomen. (Recorded initiation of 3 per minute gastric activity.)
J. W.	29	Nausea followed by eructation—vomited four minutes later.
W. G.	30	Motor response. (Initiation of 12 per minute contractions.)
	31	Motor response. (Initiation of 12 per minute contractions superimposed on 2 per minute waves.)
A. H.	32	Motor response. Inhibition of tone (relaxation).
	32	Repeated. Inhibition of tone and desynchronization of regular 3 per minute activity.

As can be seen from the above cases, abdominal sensation and changes in gastric motility and tone could be repeatedly obtained by stimulation of the surface of the island of Reil. In some cases these responses were obtained from only a single, small, circumscribed area, as in N. K. above, while in others similar responses could be obtained from the entire surface of the exposed island (Y.S.). The patient's aura might be reproduced from several points, or different types of sensation referred to the abdomen might result from stimulation of different portions of the insula.

A study of fig. 1 shows the preponderance of points giving rise to abdominal sensation over the anterior and inferior portion of the insula. In most cases when such sensation was obtained from the area posterior to the sulcus centralis, the cortex had usually proven exquisitely sensitive and similar responses had been obtained from the length and breadth of the island. Surprisingly enough, considering the localization of a gastromotor area in the anterior insula of other primates (Hoffman and Rasmussen, 1953; Kaada, 1951), alterations of gastric motor activity were recorded most often following stimulation of points immediately posterior to the central sulcus in man.

The relationship of abdominal sensation to alterations in gastric

activity is not clear. Certainly in this series, when abdominal sensation resulted from stimulation during gastric recordings, inhibitory or acceleratory changes always accompanied these sensations. Alterations in gastromotor activity might occur, however, without the patient's being aware of it.

Because of this uncertainty, we are unable to divide the insular cortex into primary gastric motor and sensory areas, although motor activity, when induced without accompanying abdominal sensation, was elicited only from the caudal portion of the insula cortex.

Abdominal sensations descriptively similar to the above have been obtained in man with some regularity by stimulation of the foot of the pre-central gyrus. The distribution of these points is somewhat diffuse, but generally they lie below and anterior to post-central areas from which sensation in teeth, gums, and jaw, tongue, and throat and inside of mouth in descending order, have been elicited. Movements of the tongue, mouth and throat are frequently produced by stimulation of this immediately supra-Sylvian area, while salivation and mastication were obtained from contiguous post-central areas. Swallowing can be produced by stimulation of the superior bank of the Sylvian fissure and taste has been assigned a probable location in the superior peri-insular cortex.

The sequential position of these acts and sensations connected with alimentation is difficult to establish. There seems to be considerable variation of functional localization among a group of patients and a complete sequence of such responses in a single patient has not been observed. Certainly the cortex of the superior bank of the Sylvian fissure and the lower end of the Rolandic region is not necessary for the production of abdominal sensation, as may be seen in the following cases:

Case G. B.—Focal epilepsy. 1. *Abdominal aura,* 2. *taste,* 3. *automatism. Electrical exploration of insula after removal of opercular banks.*

This young French Canadian was originally admitted to the Montreal Neurological Institute in January of 1945 at the age of 25. He had been kicked in the head by a horse at the age of 10 and in his 15th year had developed focal cerebral seizures characterized by sensation under the left costal margin, a bad taste in the mouth, and masticatory movements.

Operation. In February of 1945 a right temporal osteoplastic craniotomy was carried out under local anæsthesia. Although there were no abnormalities on the surface of the brain except for a few meningeal adhesions resulting from a previous operation (by Dr. Sirois of Quebec), electrocorticography demonstrated an obvious epileptogenic focus in the central region just above the fissure of Sylvius, in the vicinity of point C, fig. 2.

Some of the results of stimulation[1] are shown in fig 2.

[1]With the Thyratron stimulator.

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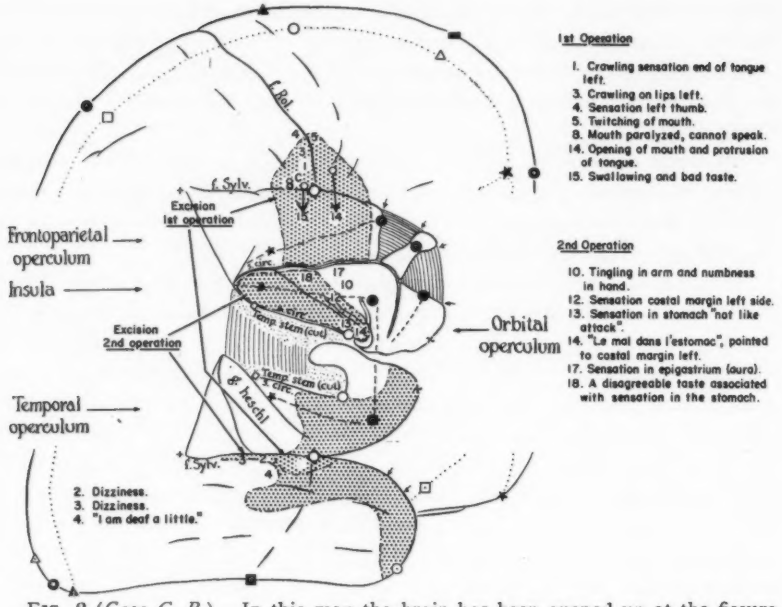
1st Operation
1. Crawling sensation end of tongue left.
3. Crawling on lips left.
4. Sensation left thumb.
5. Twitching of mouth.
8. Mouth paralyzed, cannot speak.
14. Opening of mouth and protrusion of tongue.
15. Swallowing and bad taste.
2nd Operation
10. Tingling in arm and numbness in hand.
12. Sensation costal margin left side.
13. Sensation in stomach "not like attack".
14. "Le mal dans l'estomac", pointed to costal margin left.
17. Sensation in epigastrium (aura).
18. A disagreeable taste associated with sensation in the stomach.
f. Rol.
f. Sylv.
Excision 1st operation
Frontoparietal operculum
Insula
Excision 2nd operation
Orbital operculum
Temporal operculum
f. Sylv.
2. Dizziness.
3. Dizziness.
4. "I am deaf a little."

FIG. 2 (*Case G. B.*).—In this map the brain has been opened up at the fissure of Sylvius to expose the right insula, as in fig. 6. Stippling indicates areas of cortex excised after exploration. The points that gave positive response to electrical stimulation are indicated by numbers and the responses are more fully described in the text.

1 Sensation described as crawling at the end of the tongue on the left side. There was a little twitching of his lower lip.

3 Sensation: "It was like something crawling on the lips on the left side."

4 Sensation in the left thumb and the tip. There was a little twitching of the left hand.

5 Twitching of the mouth on the left side. Patient said, "I was not able to answer."

1 Repeated. Patient said, "Tip of my tongue—crawling sensation."

8 This is on the edge of the fissure of Sylvius. Patient said, "Yes, my mouth was paralysed." There was no movement. He seemed to be trying to speak before he did so.

In summary, stimulation of the lower central region outlined the face area quite clearly. After removal of the inferior central cortex was begun, stimulation was carried out below the surface of the cortex.

14 Stimulation 1 cm. above the fissure of Sylvius on the precentral gyrus 1½ cm. below the surface produced opening of the mouth and protrusion of the tongue.

15 Stimulation of the post-central gyrus at the border of the fissure of Sylvius at the depth of 1 cm. from the surface was followed by swallowing and

patient complained of a bad taste in his mouth. He said this was the same as he had before his attack.

The lower ends of the precentral and postcentral gyri were then removed up to the sensory area of the thumb and this dissection was carried down to the surface of the island of Reil. One convolution, deep in the fissure of Sylvius and quite near to the insula, was atrophic. His post-operative course was uneventful and he was discharged with no other neurological defect than a lower left facial weakness.

He was readmitted to the Montreal Neurological Institute in March 1946, complaining of continuing epileptic seizures. These seizures were characterized by the aura of "bad sensation" under the left costal margin. Interestingly enough, the gustatory aura which had formed a part of his former attacks no longer occurred during his seizures.

His former craniotomy was reopened under local anæsthesia. The surface of the cortex appeared normal with the exception of his previous operative removal. Stimulation of the temporal lobe failed to reproduce his aura and stimulation of the edges of the previous cortical defect produced no response whatsoever. The first temporal convolution was then removed well down to the tip and a small amount of cortex was excised from the edges of the previous removal, thus exposing a major portion of the island of Reil. Stimulation of the insula was then carried out.[1]

10 Stimulation on the surface of the Island of Reil above the middle cerebral artery caused the patient to exclaim that he had a sensation in his left arm. He explained that it was tingling in the arm and numbness in the left hand.
12 Stimulation produced sensation at the costal margin on the left side.
13 Sensation returned again. When asked, he said it was not exactly like before an attack.
14 "Le mal dans l'estomac," but he pointed to the same place—costal margin, left.
12 Repeated. "I feel myself going." "Faiblesse." When asked, he said it was not like his attacks.
17 Sensation in epigastrium. When asked if it was the same as the beginning of his attacks, he said yes. The posterior and inferior portion of the island of Reil was then removed, exposing an insular convolution above.
18 Stimulation of this exposed convolution at 18 produced "Un goût curieux," a disagreeable taste, like what he had experienced before the first operation, accompanied by a sensation in his stomach. This was repeated twice. This convolution was then also removed.

This case demonstrates the repeated reproduction of the patient's gastric aura from the surface of the island of Reil following excision of the inferior Rolandic region and superior bank of the Sylvian fissure.

[1]Stimulation was carried out with Rahm Stimulator, 60 cycle, 3 volts, at point 10, 1 volt at 11–14, and 2 volts at 12 repeat, 17 and 18.

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It is interesting that although the sensation of taste disappeared from the patient's aura following removal of the foot of the precentral gyrus and upper bank of the fissure of Sylvius at the first operation, that stimulation of the posterior and superior portions of the insula could reproduce the entire aura, including taste and epigastric sensation, during the second procedure.

(4) *Somatic sensation.*—The sensations produced by stimulation of the insula were variously described by the patients as "tingling," "warmth," "numbness," "tightness," "vibration," "shock," and simply as "sensation." These sensations were usually contralateral, but were on occasion ipsilateral or bilateral. The head, tongue, roof of the mouth, lips, arms, hands, trunk, legs or toes were involved singly or in combination with other areas. Oral and upper extremity responses were most frequent and were often quite discrete, being limited to the tongue, lips or fingers. When such sensations involved more than one discrete area of the body surface as a result of a single stimulation, they usually spread to immediately contiguous areas, as for example from hand to arm, face to hand, toes to leg, or trunk to arm.

(5) *Case records of somatic sensation.*—In one case (A. Ki.) simultaneous sensations in the hand and leg of different qualities were described as the result of a single stimulation. On stimulation of the mid-portion of the insula, he stated that he had a "funny feeling" which had previously been described as "like I had to move it" in his left leg accompanied by a numb feeling in the left hand. A prior stimulation immediately anterior to this point had resulted in an epigastric sensation accompanied by the same peculiar feeling of desire to move the foot. It is probable that both of these responses represented spread to the second sensory area on the superior bank of the Sylvian fissure.

Since there seems to be some variation in the spatial distribution of cortical areas yielding similar responses among individuals, the topographical analysis of a group of responses such as this presents some difficulty. Despite these individual variations an indefinite pattern can be seen in the distribution of somatic sensory responses on the island (*see* fig. 3).

Immediately about and posterior to the inferior portion of the sulcus centralis insulae appears a zone in which stimulation caused the patient to experience sensation in the upper extremity. These sensations were invariably contralateral and were usually confined to the hand or a portion thereof, the fingers alone being involved on several occasions. In one patient, spread was noted to the arm, and in another, to the trunk.

Sensations produced by stimulation anterior to the central sulcus

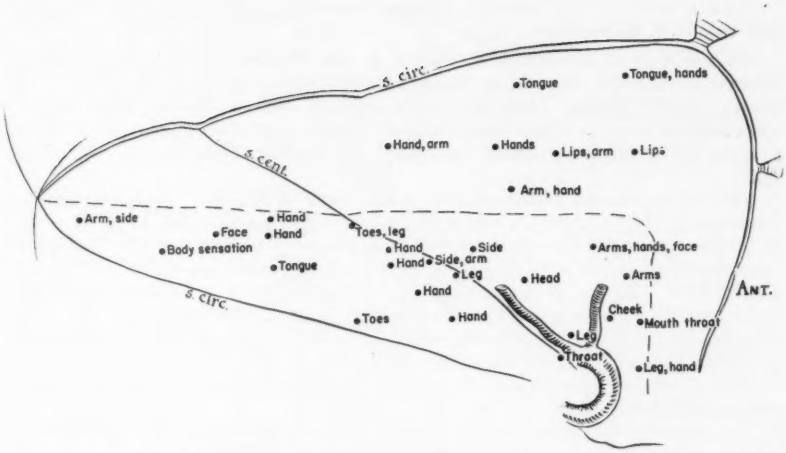

FIG. 3.—Somatic Sensory Responses—Insula. Points of stimulation which produced somatic responses on right and left sides are transferred to this map of the right insula. The anterior end is to the right, posterior to the left. S. cent. = central sulcus, S. circ. = circular sulcus. The broken line separates the portion of the insula covered by the parietal and frontal opercula, above and in front, from the portion covered by temporal operculum below. The upper extremity responses, below and posterior to the central sulcus, were all contralateral. Above the central sulcus and anterior, the responses were chiefly midline and when there was spread it included both arms (*see* text).

seemed to differ in several respects from the above. These sensations were usually referred to mid-line structures such as lips, tongue, mouth, and throat and were usually bilateral in distribution. Spread of these midline sensations to one or both upper extremities was noted on occasion. When stimulation in this anterior zone produced sensation in the upper extremities alone, this too was usually referred bilaterally, although contralateral and ipsilateral responses did occur. Stimulations producing sensation in the lower extremities were too infrequent and scattered to permit definite localization although they tended to be situated in the more inferior portions of the exposed insula.

Opportunity for exploration of the entire insula of one individual has seldom occurred. In only one case were sufficient somatic sensory responses obtained to give some indication of topographical relationships in a single patient. This case (B. McK.) has been presented, in part, in an earlier publication (Penfield and Jasper, 1954, p. 84), but the case has so many interesting features of insular and peri-insular response that it warrants discussion in greater detail at the present time.

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Case B. McK.—Focal epilepsy. Seizure pattern—1. Abdominal aura, 2. sensation in lips, 3. automatism.

This woman of 28 years was referred to the Montreal Neurological Institute because of epileptic seizures in January 1949, by Dr. W. D. Nunnally of Fairmount, West Virginia. She had had a febrile illness at the age of 18 months associated with major convulsive seizures. Beginning at the age of 4 she began to have recurring "blank spells" preceded by a feeling of numbness in hands and lips.

On admission, the pattern of each attack was as follows: (*a*) A sensation of "movement" in the abdomen which she said was apt to end in belching by mouth, or the passage of gas through the rectum. (*b*) Before or after the onset of abdominal sensation she had a "peculiar sensation" in her lips, together with a sensation in the terminal portions of both hands. (Fingers and distal portion of the palms.) Occasionally she also experienced a sensation in the epigastrium and throat and flushing of the face. (*c*) These minor attacks were occasionally followed by automatism or by a major convulsive seizure.

There was electrographic abnormality in the right fronto-temporal region which consisted of slow and sharp waves.

Osteoplastic craniotomy under local anæsthesia showed no obvious superficial abnormality except that the first temporal convolution was narrowed anteriorly. The cortex was explored electrically in some detail using a gentle electric current. Points from which stimulation[1] produced positive responses are indicated by numbers in Fig. 4. Great care was taken to verify these results by stimulating from time to time without warning the patient and also by warning the patient without stimulation.

Stimulation of that part of the lower end of the precentral gyrus from number 23 down to 17 and 18 gave responses characteristic of the second sensory system. These responses were unusually detailed due, no doubt, to sensitization by epileptic discharges. The surgeon hoped they would guide him in his proposed excision. Consequently time was taken to record them in detail and the accuracy of the responses was verified by occasional stimulation without warning, and by warning her when no stimulation was made.

The following second-sensory responses came from just above the fissure of Sylvius, as shown in fig. 4:

17 Repeated. Patient said there was a wave beginning in the tips of the fingers of the left hand which passed up her arm and down her side to halfway between knee and hip. Confined to left side.
17 Repeated after an interval. Sensation in arm, but she was able to move arm and fingers during the stimulation.
17 Repeated. Tingling in arm and down almost to knee.
18 A "tautness" which began in her shoulder and went into her fingers. When asked, she said the sensation was like "a faint tingling and then it wanted to draw."
18 Repeated. The patient had the same sensation very slightly but was able to touch Dr. Pasquet's fingers as accurately during as before stimulation.
19 Sensation in third finger.
19 Repeated. Sensation in second and third finger.

[1]Stimulation was carried out with a Rahm Stimulator 60 cycle. 1·5 volts at points 1 to 22, 2 volts at points 23 to 26, 3 volts at points 28 to 31, 2 volts at points 32 and 33, 3 volts at points 34 to 38.

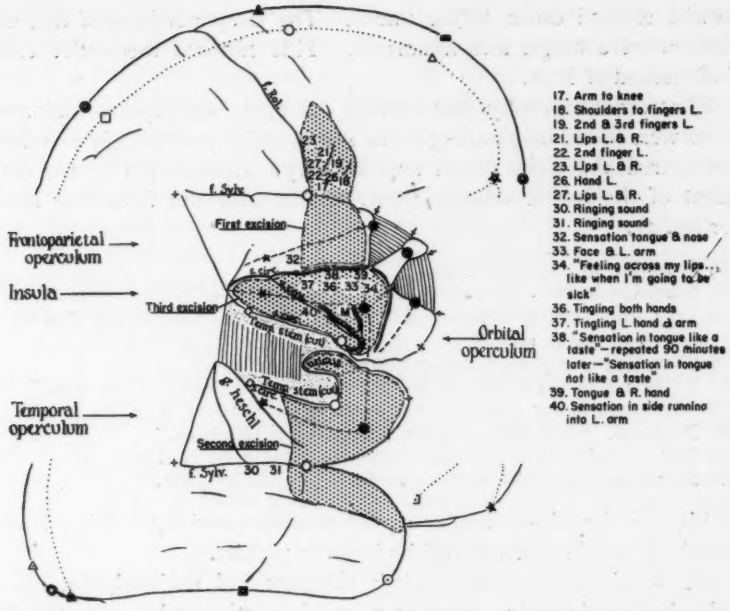
f. Rol.
f. Sylv.
First excision
Frontoparietal operculum
Insula
Third excision
Orbital operculum
Temporal operculum
Second excision
f. Sylv.
17. Arm to knee
18. Shoulders to fingers L.
19. 2nd & 3rd fingers L.
21. Lips L. & R.
22. 2nd finger L.
23. Lips L. & R.
26. Hand L.
27. Lips L. & R.
30. Ringing sound
31. Ringing sound
32. Sensation tongue & nose
33. Face & L. arm
34. "Feeling across my lips... like when I'm going to be sick"
36. Tingling both hands
37. Tingling L. hand & arm
38. "Sensation in tongue like a taste"—repeated 90 minutes later—"Sensation in tongue not like a taste"
39. Tongue & R. hand
40. Sensation in side running into L. arm

FIG. 4. (*Case B. McK.*).—The fissure of Sylvius of the right hemisphere has been opened up as in fig. 6. Numbers represent stimulation points which yielded positive response. Stippling indicates areas excised after exploration. The numbered points on the superior bank of the fissure of Sylvius gave responses which must be called "second-sensory." Those on the insula were the same. Much of the second-sensory area remains untouched on parietal operculum posterior to the excision (*see* text).

21 "Unlike feeling in my lips. As though my lips were hollow. Nothing like attack."
22 Tingling feeling in index finger.
23 "Slight movement in my lips." Nothing observed.
26 Tingling and numbness left hand, all over.
27 "Light feeling in my teeth transferred to my lips."

These responses were typical of those elicited by stimulation from the second sensory area in man, but none seemed, to the patient, to be identical with the auras which preceded her attacks (abdominal aura, sensations in lips and finger tips). There was electrocorticographic abnormality on either side of the fissure of Sylvius which suggested a deeper focus of discharge.

Consequently the second-sensory cortex was removed by suction and the removal carried down the superior Sylvian bank to the insula, as shown by the stippling in fig. 4. The first temporal convolution was

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likewise excised down to the uncus. The deep portions of this convolution were tough and abnormal. This exposed the entire extent of the island of Reil.

Electrocorticography was carried out again and spikes and sharp waves were found originating in the insula which was grossly abnormal, discoloured and quite tough and leathery. Stimulation of the entire extent of the insula was then carried out with the following results (*see* fig. 4):

32 Sensation in tongue and nose.
33 Sensation in face, apparently above lips. Some feeling in left arm.
34 Very slight feeling across lips. "This is the first time it felt like when I am going to be sick."
36 "Tingling in my hands, more marked on left."
37 "Tingling in the fingers of my left hand which moved up the arm."
38 "Sensation in my tongue like a taste. I never tasted it before."
38 Repeated. "Odd feeling in my tongue. Not like taste."
39 Odd sensation in tongue and fingers of *right* hand (ipsilateral).
40 Sensation in the side of body running into the left arm.

Finally the whole insular cortex was removed by suction leaving the middle cerebral artery and its branches intact.

No gastric records were made in this case and, curiously enough, no abdominal or visceral responses resulted from stimulation. On the other hand, second-sensory responses were produced from both sides of the chief second-sensory area within the fissure of Sylvius. Stimulation of cortex above the fissure of Sylvius gave an unusual number of responses, and after removal of this area similar responses were obtained by stimulation of the insula, where nearly all the positively responding points were on the superior border of insula. Not all of the superior operculum had been removed and stimulation of the untouched surface of the Sylvian bank, where it could be reached at point 32, gave typical second-sensory responses.

Our conclusion is that epileptic conditioning had rendered second-sensory areas on the superior Sylvian bank stimulable from a distance. This might be considered distant activation of this area from stimulation of these two neighbouring areas. On the other hand one might argue that the second-sensory area of cortex actually extends from the lateral surface of the hemisphere above, down the superior Sylvian bank onto the surface of the insula.

(6) *Results of ablation.*—Unilateral removal of the temporal portion of the insular cortex by suction can be easily accomplished following anterior temporal lobectomy. Total excision of the insula is somewhat more difficult and initially it was attempted only after the removal of

the overlying opercula, as in the case of B. McK. just described. Elevation of the intact superior opercular banks is a somewhat dangerous procedure and should be undertaken only when obviously necessary. Nevertheless the cortex of the insula was removed completely in four cases of this series.

No immediate somatic sensory or motor or visceral sensory effects followed either partial or complete unilateral excision of the island of Reil, nor could any subsequent neurological deficits be attributed to loss of this structure. Gastric recordings were made during the partial excision of the insula in one case, and no alteration of gastric motility or tone was observed in that case. But in another case, W. G., to be described below, total unilateral insular ablation caused immediate marked alterations of gastric motility and tone as shown below.

Case W. G. Focal cerebral seizures, gastromotor recording during stimulation of insula and during insulectomy.

This 41-year-old man entered the Montreal Neurological Institute in November 1953 with a history of difficult birth, a head injury at 20 years of age, and epileptic seizures for the past twenty years.

His attacks were characterized by a warning sensation about the left eye, followed by what he called an explosion of light and a griping sensation in the periumbilical region, rising to just below the manubrium. These sensations might be followed by automatism and amnesia. He had had three generalized convulsions.

The only neurological defect noted on admission was a left upper quadrantic homonymous hemianopia.

A right temporo-parietal osteoplastic craniotomy was carried out under local anæsthesia. A large cyst, replacing the second and third temporal convolutions was found and removed with the remainder of the temporal lobe and part of the occipital lobe, which was also abnormal, as shown by electrocorticography.

The exposed insular cortex was markedly atrophic, tough and yellow.

Initial exploration of the insular surface with the stimulating electrode at a potential of 2 and 3 volts[1] gave no response. At 4 volts acceleratory changes were noted in the electrogastrogram from points (16A and 16B, fig. 5) over the middle and posterior surface of the exposed insula. The effect produced by stimulation of both points was identical, and consisted in the sudden onset of 12 per minute gastric contractions once from a resting state and once from a regularly occurring 3 per minute activity which had persisted throughout most of the operation. These gastromotor alterations occurred without the patient's being aware of any sensation.

Complete removal of the insular cortex by suction was then carried out. During the last stage of this removal the electrogastrogram showed a sudden and complete inhibition of the previously existing regularly occurring 3 per minute pyloric contractions and a fall in gastric tone. Both of these effects persisted for several minutes. Irregular 1 per minute contractions, dissimilar to any gastric activity previously recorded, then appeared and persisted to the end of the record.

[1]Square wave generator 60 cycle.

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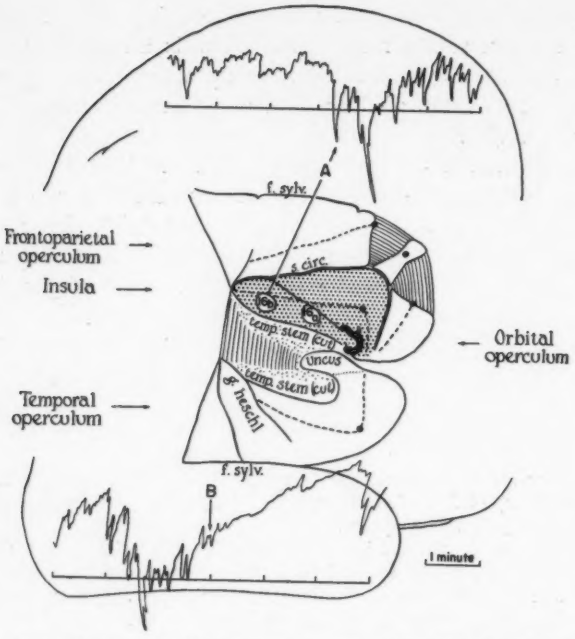

FIG. 5 (*Case W. G.*).—A, The upper tracing shows the effect on the electrogastrogram produced by insular stimulation at 16*b*. B, The lower tracing shows the inhibition of pyloric activity subsequent to ablation of the insula. The excision of insular cortex is indicated by the stippling.

This phenomenon seems significant since ablations of portions of temporal, parietal, frontal and occipital cortex in other patients failed to alter the pattern of gastric activity. Unfortunately, the opportunity did not arise during the present series to observe the effects of ablation of those anterior limbic and frontal areas, the removal of which has been observed to have a profound effect on gastric motor function in animals (Babkin and Kite, 1950; Mettler, Spindler, Mettler and Combs, 1936).

DISCUSSION

It has long been a difficult task to delimit the functional areas of cortex within the fissure of Sylvius and in the circular sulcus that surrounds the insula. Tentative conclusion in regard to the insula of man and the hidden walls of the opercula which surround it have been mapped out by one of us (W. P.) as shown in fig. 6.

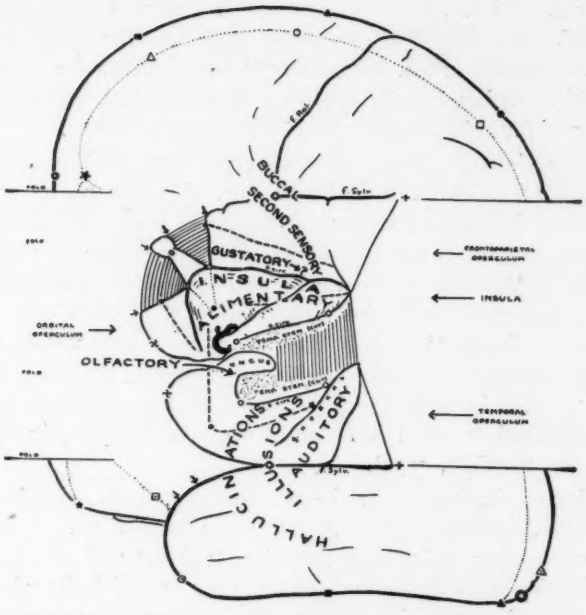

FIG. 6.—Functional areas in insular and circuminsular regions. Some of the boundaries which separate these areas from one another are, as yet, not clearly established. (Reproduced from Penfield and Jasper (1954) fig. X-3, p. 426.)

The purpose of this present study was to examine the relationship of the island of Reil to the gastro-intestinal tract more critically by means of an electro-gastrograph which could be passed into the patient's stomach before operation with a minimum of discomfort.

In fig. 6, the opercular walls are laid open all around the insula, and it may be seen that this island of cortex is quite continuous with the frontal and parietal cortex in front and above, and with the temporal cortex below, while Heschl's transverse gyrus adjoins it posteriorly.

It is to be expected, therefore, that local epileptic discharges might cause the patient to experience sensations due to activation of one after another of these functional areas. Indeed gustatory and olfactory sensations might well be counted as the special senses most closely allied to the alimentary system and the buccal and pharyngeal sensory areas of the superior Sylvian Bank form part of the alimentary representation.

Our previous studies have left us in doubt as to the exact limits of localization of the second sensory system and have led us to wonder

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whether or not the second sensory cortex in man may cover part of the insula itself. We hoped in this paper to decide this question as well as to prove whether or not the insular cortex exerts motor control over the stomach. Before considering these questions we will add a short description of the neighbouring functional areas of cortex.

(1) *Circum-insular cortex.*—The temporal operculum constitutes the superior surface of the temporal lobe (fig. 6). The posterior portion of this surface is auditory-sensory and perhaps also vestibular-sensory. The portion anterior to this frequently gives rise to psychical responses on electrical stimulation or when subjected to epileptic discharge. These psychical responses may be *experiential* (hallucinations of past experience) or *interpretive* (illusions of present interpretation). The uncus very occasionally yields an olfactory response but the grey matter beneath it, which includes the amygdaloid nucleus, regularly gives rise to ictal automatism when it becomes the site of epileptic discharge[1] (Feindel and Penfield, 1954).

Anterior to the insula, in the orbital operculum, stimulation may produce respiratory changes. Above is an area of cortex devoted to gustatory sensation and also to sensation in throat and mouth. On the superior bank also is the second-sensory area in which the whole body, the face and all extremities seem to find some sort of representation. We have not yet been able to reach a conclusion as to the limits of the second-sensory cortex and its relationship to sensory cortex devoted to mouth and pharynx. Coming out to the lateral surface of the hemisphere where the post central gyrus meets the fissure of Sylvius, salivation and contralateral mouth sensation have a localization.

(2) *Causes of confusion.*—Thus it is not surprising that the results of stimulation of the insula are confusingly varied since it is surrounded by such a remarkable variety of functional areas. It follows, too, that local epileptic discharges often produce a great variety of seizure patterns.

Another cause for confusion is the fact that in many of our patients there are atrophic lesions which date from early years of life. Such lesions may distort the normal relationships of the cerebral cortex because there are displacements of convolutions during growth and possibly migrations of functional areas. It is especially difficult to predict the shift of functional areas which may result from the presence

[1]We have long suspected that there is some sort of a motor mechanism close to the insula, located perhaps in the temporal lobe itself, since local discharge often causes the patient, during a temporal lobe seizure, to make tonic and postural movements of extremities, body and face.

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of such lesions in and about the Sylvian fissure, where such a complex infolding of cortex takes place during development and growth.

Any area of cortex which has been subjected to years of epileptic discharge is apt to respond more readily to electrical stimulation than normal areas. This may be called epileptic facilitation. It may result at times in response of one area of cortex to the stimulation applied to a neighbouring area.[1] Thus, neighbourhood responses may result from stimulation when the electrode is applied to an area which, at the moment, is less responsive to stimulation.

As might be expected, therefore, stimulation of the insula in these epileptic patients evokes multiple and sometimes confusing responses—visceral sensory and motor, somatic sensory and motor, respiratory arrest, sensations of taste and smell and hearing, psychical illusions and mental confusion. But among all the types of response, only two seemed to be statistically important (*a*) the visceral (sensory and motor) and (*b*) the somatic (sensory).

(3) *The alimentary system.*—More than a third of the stimulations of the insula caused sensation to be referred to the abdominal cavity. The gastromotor recording throws some light on the matter. In several instances, evidence of alteration of gastric motility was recorded either during such sensation or as a separate event without accompanying sensation. Subsequent ablation of the insular cortex in one case caused profound alterations in gastric motility. It has further been demonstrated that such visceral responses may be obtained by stimulation of the insula after removal of the adjacent supra-Sylvian and temporal cortex (Case G. B., fig. 2). This evidence would certainly seem to indicate that the island of Reil has some sort of motor control over gastro-intestinal function without neuronal detour to adjacent cortical areas.

Since the patient was sometimes not aware of any abdominal sensation during unquestioned gastromotor responses it is obvious that if the electrogastrograph had been employed in more of the patients, reported here, the visceral responses would have been proportionally more frequent.

[1]In the past, during exploration of the cortex of epileptic patients this was found to be marked in frontal and parietal lobes. The displaced response was usually somatic sensation or occasionally a facial movement. We have called such unexpected results "distant responses" (Penfield and Boldrey, 1939).

Even in the normal cortex the facilitation of motor response by preceding stimulation and the obtainment of that response from a distance during the continuance of the facilitation effect, as described by Sherrington and Graham Brown in the mammalian cortex, may be reproduced for sensory and psychical areas in the cortex of man. One may assume that the hyper-responsiveness of the human epileptic cortex depends upon inter-ictal neuronal discharges.

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Because of the limitations imposed by the therapeutic approach in human beings, exploration of the entire region suspected of subserving alimentary function has not been possible in a single patient. As a result of these limitations we have not been able to demonstrate, in one individual, a sequence of alimentary motor events similar to that obtained in the dog by Babkin (1951).

A summary of results obtained from a number of patients, however, seems to give some indication that such a pattern exists both motor and sensory. Just above the fissure of Sylvius, and extending down into it, are representations of chewing and swallowing and salivation; sensation of mouth and pharynx are found on the opercula and taste has a representation in a zone where the upper Sylvian bank joins the insula.

Unfortunately, sufficient variations exist between individuals, either normally or as a result of pathological alterations, to make this sequence sometimes indefinite. For example, taste may be obtained by stimulation of well defined points on the insula, as might swallowing or sensation in tongue or throat in other individuals.

It seems to be clear, however, that bilateral sensation in the upper part of the alimentary tract including taste, as well as movements (such as swallowing and eating) are "represented" in the cortex above the insula and that movements of stomach, and probably intestine, can be controlled by the cortex of the insula.

(4) *Somatic sensation.*—Visceral sensation is frequently the result of epileptic discharge arising in the Sylvian fissure, but somatic sensations are noted comparatively infrequently in the complex of psychical, motor and sensory events, which may form parts of epileptic seizure patterns. It was surprising, then, to find that somatic sensation was elicited from the insular cortex almost as frequently as visceral sensation.

These somatic sensory responses were first thought to represent spread of the stimulating current upward along the opercula, above, to the second-sensory cortex (fig. 7). In some instances this may be true, but a certain amount of evidence exists to suggest that it is not always the case.

The quality of somatic sensation produced by stimulation of the insula does not differ very much from that elicited from Rolandic and supra-Sylvian sensory areas. Feelings of tingling, numbness, warmth and movement were described. As with stimulation of the second-sensory area, these sensations are sometimes referred to contralateral or ipsilateral parts of the body, and sometimes to bilaterally symmetrical

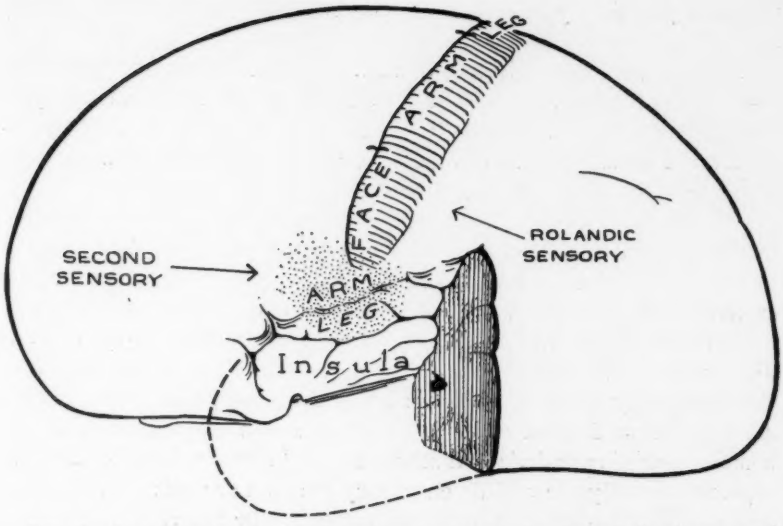

FIG. 7.—Localization of second sensory representation (stippled) of arm and leg on superior bank of fissure of Sylvius of man. It is probable that there is a face representation above arm and that the stippling should be carried more posterior within the Sylvian fissure and down to the insula. (Reproduced from Penfield and Jasper, 1954, fig. III-27, p. 87.)

areas. The desire to move or tendency to move which may result from secondary sensory stimulation was reported from only one insular stimulation. The inhibition of voluntary control which occasionally accompanies such a second-sensory stimulation elsewhere (Penfield and Jasper, 1954), was not observed in the insula.

Our analysis is greatly handicapped by the fact that the superior portion of the insula has been so rarely exposed. In the case of B. McK. (fig. 4) the whole insula was uncovered. The results of stimulation of the lower end of the precentral gyrus and the upper margin of insula, after removal of the lower precentral gyrus, were quite similar. If the first was a distant or neighbourhood response, it seems likely that the second was also and that the stimulation in both areas served to excite a second-sensory area situated a little more posterior on the upper Sylvian bank.

If, as is suggested in fig. 7, there is a localization of arm above leg, on the upper bank of the fissure of Sylvius (a conclusion that is in agreement, with the findings of Woolsey in the monkey), it might be expected that leg responses, on the insula, would be more frequent than face or upper extremities. However, the findings on the insula

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represent just the opposite state of affairs. Leg responses there are too rare to be given any localization.

In the chart, fig. 3, it may be seen that, posteriorly and below the sulcus centralis insulæ, there is an area in which sensation was produced in the upper extremity. These sensations were invariably contralateral and usually confined to the hand or a portion thereof, the fingers being involved alone on several occasions.

On the other hand stimulations anterior to the central sulcus produced bilateral sensation in mid-line structures such as lips, tongue, mouth and throat. When sensation was produced in the upper extremities in this area it was usually bilateral.

It is an interesting fact that in only one case (A. Ki.—4 in fig. 1) did somatic and visceral sensation result from a single application of the stimulating electrode to the surface of the insula, this response being a detailed reproduction of his habitual aura. In other cases, although somatic sensation and visceral sensation might be obtained from points separated by only a few millimetres, they were not evoked simultaneously and spread did not occur from one system to the other.

Summary and Conclusion

Information, derived from the stimulation and removal of the insula of man, has accumulated during the past ten years since the publication of case J. C.[1] whenever opportunity permitted. This evidence has now been reviewed by one of us (M. E. F., Jr.) and new methods of observation employed.

More than one-third of the positive sensory responses to stimulation of the insula consisted in sensations that resemble the responses to stimulation of the superior bank of the fissure of Sylvius, responses considered to be second-sensory. The decision as to whether this is an evidence of neighbourhood activation or whether some part of the insular cortex is involved in a somatic sensory mechanism must be left an open question.

Gastric recording, by means of an electrogastrograph and an intragastric rubber balloon during operation, has demonstrated clearly that,

[1]The case J. C. was described in the Ferrier Lecture of 1946 (Penfield, 1947). J. C. had seizures ushered in by a strange feeling in the abdomen associated with audible intestinal peristalsis. At operation, stimulation of the insula (following partial temporal lobectomy) caused her to feel the familiar abdominal aura, referred to the umbilicus, following which she said she was "going to bring up gas." Partial removal of the insula was carried out. In the nine years since operation she has had no further "auras" and no attacks and the alimentary system has functioned normally.

in conscious men, the island of Reil can exert a control over gastric motility and stomach tone.

Electrical stimulation of the insula produced, in 4 out of 6 cases, undoubted effects upon the stomach. These effects varied from complete inhibition of gastric motility to the production of violent activity with marked increase in tone. Tone changes might accompany, or appear independent of, alterations in rate of stomach contractions.

In this series of observations, whenever abdominal sensation was produced by stimulation during gastric recording, there was some concomitant change in gastric tone or motility, either inhibitory or acceleratory. On the other hand motor effects were sometimes produced without accompanying sensation.

It must also be left an open question as to whether abdominal and epigastric sensation has any representation in this region independent of the changes produced in motility and tone of the gastro-intestinal system. Somatic sensation and abdominal sensation may be produced by stimulations of near-by points on the insula but they are not produced simultaneously during one application of the stimulating electrode.

Complete insulectomy produced inhibition of the previously existing 3 per minute pyloric contractions and a fall in gastric tone (case W. G., fig. 5). This occurred toward the end of excision. A few minutes later, irregular 1 per minute contractions were set up, unlike any gastric activity previously recorded, and continued several hours up to the end of the recording. There were three other total insulectomies but gastric recording was not being carried out during the procedures.

Control studies of gastric motility during similar operations when other parts of the cerebral cortex were stimulated or removed gave no evidence of motor responses.[1]

More than one-third of the positive sensory responses to stimulation of the insula consisted in an abdominal feeling of some sort and it is assumed that most, if not all, of these sensations are secondary to motor change in the gastro-intestinal tract.

[1]This statement must be qualified as follows: On two occasions there was arrest of the gastric activity which was being recorded at the time of stimulation of some extra-insular cortical point, once on the postcentral gyrus and once on the hippocampus. On neither occasion was there any associated gastric sensation. When each of these points was re-stimulated the apparent result was not repeated. We must assume that the cessation of gastric activity was coincidental or possibly due to spread of discharge.

On the other hand no positive motor phenomena (imitation of gastric activity or increase in rate or tone) were observed as the result of several hundred extra-insular stimulations while gastric motility and tone were being recorded.

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VESTIBULAR EPILEPSY

BY

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"VERTIGO does not bereave the patient of his senses nor affect him with convulsions." This is still a widely held diagnostic rule first formulated in the second century A.D. by Soranus of Ephesus. There are, however, exceptions and these are the subject of this communication.

On recovery of consciousness following an epileptic fit, a few individuals, for a variable period, experience vertigo which is occasionally associated with tinnitus. This post-ictal vertigo may be of disabling degree, making locomotion impossible for periods of from a few minutes to an hour. As a rule similar vertiginous sensations, often provoked by quick movements, are also experienced between fits.

Unlike pre-ictal vertigo, post-ictal vertigo is a rare clinical phenomenon, and this was confirmed by questioning a large control group of epileptic subjects. Furthermore, a study of the case-histories does not reveal that cerebral lesions giving rise to epilepsy with vertiginous aura are associated with post-ictal vertigo. These negative points suggest that post-ictal vertigo is not an integral part of the epileptic phenomenon. On the other hand the constant association between post-ictal and inter-ictal vertigo already mentioned, points to a common underlying mechanism. The occasional linkage with tinnitus or deafness, as also the ready provocation of vertigo by movements of the head and other clinical features revealed by analysis of a number of these case histories, suggest that the inter-ictal vertigo has a vestibular origin. Bearing in mind, then, the common mode of origin of inter-ictal and post-ictal vertigo—and the cases quoted subsequently seem to justify this inference—it must be assumed that both these forms of vertigo are engendered by activation of the vestibular apparatus. This conclusion is further supported by those case histories which, in addition to inter-ictal and post-ictal vertigo, also have clear evidence of vertigo immediately before the commencement of the fits.

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If the vestibular origin of pre- and post-ictal vertigo is accepted, the ictus also can be reasonably regarded as having been precipitated by the vestibular activation, and "vestibular epilepsy" is the suggested designation of this nosological entity. The epileptic nature of the attacks is indicated by loss of consciousness, often protracted—in the absence of obvious disturbance of circulation—and the occurrence of convulsions in some cases. Some attacks have been personally witnessed, and the absence of any cardiac or vasomotor disturbances confirmed. It may be mentioned that virtually all the cases introduced here were referred with the provisional diagnosis of epilepsy.

The syndrome of vestibular epilepsy has been subdivided into three main groups to bring out certain nosographic characteristics without implying that any fundamental pathophysiological differences exist. Study of the case histories indeed reveals that individual patients may be subject to attacks which, according to the classification adopted here, fall into several different groups. This study is based on a clinical analysis of 39 personally observed cases, of which representative examples have been selected for publication.

GROUP A.—The diagnostic feature of this group is a post-ictal vertigo, with or without tinnitus, or occasionally post-ictal dysequilibrium.

GROUP B.—Cases in this group differ from those of the previous group only in the absence of post-ictal vertigo. All these patients exhibited pre-ictal vertigo, and some evidence of labyrinthine disturbance between fits.

GROUP C.—A history of inter-ictal vestibular disturbances and of epileptic fits without warning and without vestibular symptoms in their wake are the clinical features of this group.

GROUP A.—Cases in this group can be further subdivided into those with vertiginous or acoustic sensations prior to the seizure and those without any warning. A clear history of post-ictal vestibular disturbances provides the touchstone for the diagnosis of this group. Very rarely transient tinnitus may be the only significant post-ictal phenomenon.

Case 1.—Male, aged 59.—One month following a relatively slight head injury he began to have "blackouts" at irregular intervals. Some of these occur without any warning, and according to his wife "he suddenly loses himself—sits there, eyes staring, and opens and shuts his mouth—his colour is grey." Duration varies from approximately five to twenty minutes. Afterwards "helpless" for some time. On recovering consciousness he becomes aware of a "buzzing sound" in the left ear, and at the same time "I feel horrid—I am going round and round—horrid dizzy feeling—weird sensation, as though something is whirling; I feel as though I am

drunk; there is usually a headache; the weird feeling goes off when the buzzing stops." Some of his "blackouts" are preceded by an exactly similar vertiginous sensation and tinnitus. Sometimes he has experienced "a nasty buzzing, headachy dizziness" associated with weakness of lower limbs without, however, loss of consciousness. Investigations, which all yielded negative results, included EEG, air encephalography, C.S.F. examination, and radiography of skull and chest. During the period of observation, extending over 2½ years, his hearing remained normal and attacks continued to occur.

Past history.—Two years prior to the accident pleurisy and hæmoptysis.

Case 2.—Female, aged 28.—During the past year had about ten to twelve attacks. Most of them began suddenly with "a loud buzzing in my ears, especially the right ear." This is immediately followed by loss of consciousness of about 15 to 25 minutes. On recovering consciousness "everything whizzing round me, horrible feeling as though things are coming to hit my face, I feel sick, can't focus, fall about if I try to stand up." Her mother witnessed the first attack and stated that "one side of her face was pulled over." Since the first seizure she has also noticed dizziness on stooping—"usually have to grip something to steady myself."

Family history.—Sister subject to epilepsy. General medical and neurological examinations were negative.

Case 3.—Female, aged 41.—1948: Seen on account of long-standing almost complete right deafness and periodic generalized headaches. No history of aural discharge. C.N.S. examination—nil abnormal. Diagnosis—inner ear deafness and migraine.

1951: While in cinema suddenly felt faint and immediately lost consciousness, according to relative for about half an hour. No pallor. About one week later lost consciousness in a similar manner while reading at home. On each of these occasions on recovering consciousness "there is a buzzing noise in the deaf ear, and I feel as if I am going round and round in a funnel until I get to the small part, and then feel as though I am being shot back again." Neurological examination was again negative excepting for right deafness. C.S.F.—routine examination within normal limits.

Case 4.—Male, aged 44.—Six months ago "while standing soldering I came over funny—asked my wife for a drink and then I conked out. When I came round the doctor was there and I kept going giddy-like—worse when I got up—and I stopped in bed a week."

Two weeks ago "I was walking to get my tools—felt faint—I ducked my head between my legs and then went out for about ten minutes. On coming round felt as last time—giddy—have been giddy at times ever since. Light-headed when I turn head quickly."

Both fits witnessed and were associated with generalized convulsions. Multiple lipomata on arms. Neurological and otological examinations negative. X-rays of skull and examination of C.S.F.—nil abnormal.

Case 5.—Female, aged 61.—Generalized epileptic seizures until her marriage about thirty years ago. Last four years—subject to attacks in which following a momentary sensation of "giddiness" loses consciousness for a few minutes. On recovering consciousness there is a sound of "rushing water in the head," and for five to ten minutes though fully conscious is unable to stand or walk. Feels "giddy" for several hours, during which she may vomit.

For some time past quick movements produce a momentary feeling of falling. General medical and neurological examinations negative excepting for hypertension, 200/105.

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GROUP B.—Whether post-ictal vertigo is present will clearly depend on the duration of the vestibular paroxysm and the duration of the period of epileptic unconsciousness. If the former is short or the latter is long no post-ictal vertigo will be present.

Case 6.—Male, aged 22.—Last eight years subject to sudden bouts of vertigo associated with left tinnitus and deafness, of about half a minute's duration. Frequency extremely variable—on occasions several attacks daily. May fall in these attacks without losing consciousness. At times may feel "dizzy" for several days and then liable to frequent paroxysms of vertigo as mentioned.

For the past three years subject to sudden attacks of unconsciousness preceded for a moment by "a rushing noise" in the left ear, in every way similar to that which accompanies the above mentioned attacks of vertigo. Consciousness may be lost for as long as fifteen minutes, during which time generalized twitching movements have been observed, and "eyes are fixed."

Past history.—Bilateral otorrhœa in childhood up to 12 years of age. General medical and neurological examinations negative excepting for some deafness, conversational voice heard at 8 ft. on the right side and 6 ft. on the left. Audiogram showed pronounced bilateral mixed deafness. Cold caloric test—slight depression of function, more pronounced on the left side. Serological tests were negative.

Case 7.—Male, aged 19.—Heavy colds in the head are liable to bring on earache, mostly on the right side. At these times sudden turning movements of the head are liable to provoke momentary dizziness without loss of consciousness. Since the age of 9, about a dozen "blackouts" have occurred in association with earache. These comprise a sudden feeling of dizziness followed by loss of consciousness a few seconds later. On recovering consciousness "everything is muzzy and everything sounds very loud, but the dizziness is gone." Total duration of the attacks is two to three minutes. He usually goes "white" in them and the eyes are "staring." No convulsions.

General medical and neurological examinations were negative. Hearing was good and there was no nystagmus.

Case 8.—Male, aged 64.—During the past nine years the patient had seven attacks showing precisely the same features. They usually occur on stooping, when he feels intensely "giddy" and at the same time one hand involuntarily moves up to the homolateral side of the face and both hand and face "shake and quiver" for a moment. The attacks have been approximately as often right as left sided. There is never any loss of consciousness. His last attack occurred while in the sitting position on turning his body quickly to one side. For a number of years subject to "giddiness" aggravated by movements of the head and an intermittent "fizzing noise in the head." General medical examination including "carotid massage" revealed no abnormality.

GROUP C.—In the cases instanced here the liability to inter-ictal vestibular symptoms and to fits began at approximately the *same time.* This syndrome is not uncommon and Hughlings Jackson was well aware of this. Nevertheless the clinical diagnosis of necessity lacks the degree of certitude of the groups previously mentioned. Analysis of the case histories reveals that vertiginous aura—with or without tinnitus —is not an essential feature of vestibular epilepsy, and that the occur-

rence of vestibular epilepsy bears no relation to the severity of the labyrinthine affection. The appearance of vestibular symptoms prior to loss of consciousness seems to depend on the readiness with which these symptoms are perceived at the level of consciousness, and the facility with which epilepsy is precipitated. A number of patients have stated that they invariably become aware of headache or of diplopia some appreciable time before dysequilibrium as such is recognized. The readiness with which the epileptic reaction ensues is clearly dependent on many factors, and these will be analysed later. On the bases of this clinical study of the cases it would appear that the liability to an epileptic reaction is greatest immediately following the onset of a vestibular paroxysm.

A representative case of this group is one narrated by Hughlings Jackson (1880): "A medical man told me that his first attack occurred in the streets of London. He was taken to a hospital unconscious, and remained so for three hours. Such seizures would give us a hard task in diagnosis from epilepsy. Subsequently he had attacks (of auditory vertigo) without loss of consciousness." Even when the patient is known to suffer from "auditory vertigo" the task of establishing the cause of an epileptic fit, without pre- or post-ictal vertigo, is a formidable one. Excepting for the frequency of this association, there is nothing to indicate clinically in an individual case that a link exists between these two conditions. Indeed they can, of course, be coincidental and have entirely different pathologies, as is illustrated by a patient described by Dix and Hallpike (1952).

Case 9.—Male, aged 58.—About a year ago, while in excellent health, he had his first attack without any warning. Consciousness was suddenly lost, and he sustained slight injuries. On returning home that morning from the night shift he had another somewhat similar attack. He has lost consciousness in all on three occasions. During the subsequent few weeks he had numerous slight attacks, especially on rising quicky from the recumbent position. These attacks are mainly characterized by momentary amaurosis. On turning his head backwards, or occasionally after stooping "I begin to whirl—eyes seem to roll and body topples." These disturbances are also of extremely brief duration, and are not followed by any symptoms. On two occasions he has experienced a haziness of vision followed immediately by loss of vision, and at the same time he felt "as though I was swaying a bit—I have to grab hold of something to save myself." The disturbance is of momentary duration, and on each of the two occasions it was followed by severe headaches. Occasionally when getting up sharply from the sitting position "would have to stop suddenly and sit down again to regain myself." He has enjoyed excellent health, and excepting for a period of a few weeks during the early stages of his present malady when he was feeling "rather queer," he has remained quite fit. General medical and neurological examinations revealed no significant abnormalities.

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Case 10.—Male, aged 52.—Nine weeks ago "suddenly felt like a flush of blood" in the right side of his head, "and I went down, that's all I remember." He recovered consciousness one and a half hours later in the first-aid room. During the past five weeks the patient had three further attacks, each of uniform nature. "Blood shoots up suddenly to the right side of my head—my legs are useless—head going round." He does not lose consciousness, but is quite incapable of walking. Since childhood his right hearing has been subject to considerable fluctuations, and at times is very defective. More recently he developed right tinnitus. The latter is liable to become louder in the attacks already described. General medical examination negative excepting for moderate degree of right deafness.

Case 11.—Male, aged 58.—While sitting by the fire "all of a sudden had a weird feeling in the pit of the stomach"—immediately lost consciousness for about ten minutes. Next morning a few hours after getting up became aware of left deafness, and also noticed a high-pitched hum in the left ear, and unsteadiness on turning head to the left for several days. General medical and neurological investigations negative excepting for left deafness with normal caloric labyrinthine reactions. During the following nine months he developed progressive right deafness and this necessitated the resort to a hearing aid. Caloric labyrinthine reactions remained normal.

Family history.—Sister is said to be suffering from Ménière's disease.

Seizure Patterns

In a number of cases the seizures are attended by loss of consciousness and generalized convulsions, and the epileptic nature of the attacks cannot be in doubt. (Case 4.)

Seizures which are characterized by suspension of consciousness for brief periods, with slight twitching of eyelids or of muscles of the face are also clinically indicative of epilepsy. (Case 1.) In several patients slight muscular convulsions were unilateral. (Cases 2 and 8.)

In a number of cases, as for instance in the one described by Hughlings Jackson, the periods of loss of consciousness were protracted—occasionally as long as a few hours—without any obvious convulsive manifestations. It is possible that this type of seizure, though comparable to vestibular epilepsy, is however a result of a different type of spasmodic disturbance of function of the central nervous system induced by vestibular excitation.

Unfortunately in a number of cases no eye witness accounts were available of the phenomena during periods of unconsciousness.

Nature of the Causative Vestibular Disorder

In the great majority of cases in this series one can reasonably surmise, on clinical grounds, that vertiginous paroxysms were due to functional labyrinthine disorders. Attempts have been eschewed to relate the vestibular symptoms and signs shown by patients reported here to any nosographic system of labyrinthine disorders, mainly

because the available knowledge of labyrinthine pathology is too meagre to make this rewarding.

Diagnosis

Even after excluding from consideration cases of vestibular epilepsy classified here under Groups B and C—cases in which the clinical diagnosis must of necessity be uncertain—experience suggests that the condition of vestibular epilepsy is fairly common, and it has therefore not escaped the attention of clinicians in the past. Gowers alludes to these cases without, however, subscribing to the epileptic pathogenesis as the following quotation reveals: "A special difficulty, however, is presented by some cases in which attacks, really labyrinthine in origin, present a misleading resemblance to those of epilepsy" (Gowers, 1901). Hughlings Jackson on the other hand clearly accepted their epileptic origin when he wrote: "In some cases of epilepsy and epileptiform seizures there is organic ear disease and probably a causative relation," and again in the same paper: "We may put in that the ear is at fault and that the centres suffer." (Jackson, 1880.) Hughlings Jackson also recognized "epilepsy with auditory warning" and "epileptic vertigo." On many occasions in his writings he makes reference to "epileptic vertigo," which he defined as follows: "I mean real vertigo, a sensation of movement of external objects (or of himself turning) at the beginning of some severe attack of epilepsy proper" (Jackson, 1879). Hughlings Jackson clearly implied that these epilepsies are characterized by auditory and vertiginous auras respectively. It is necessary, therefore, to draw a distinction between epilepsy with an acoustic or vertiginous aura on the one hand and cases of epilepsy similarly preceded by tinnitus or vertigo but in which these sensations, however, originate in the vestibular and cochlear systems. Unilateral tinnitus can be a feature of both vestibular epilepsy and "epileptic vertigo." Pre-ictal vertigo of vestibular epilepsy and vertiginous aura of "epileptic vertigo" are usually of equally brief duration. In the differential diagnosis consideration must be given to the following points:

(1) Sensation of rotation is on the whole rare as a feature of aura of temporal lobe epilepsy. Electrical stimulation of the temporal cortex (first temporal convolution) provokes only mild equilibratory sensations as compared with the violent responses to direct stimulation of the vestibular labyrinths. "The most common description was that of a sense of movement of the whole body. Only once was nausea produced and, considering that nausea is a frequent result of stimulation of the island of Reil beneath this area, it may have little significance here" (Penfield

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and Rasmussen, 1950). The following brief notes illustrate unilateral tinnitus associated with dysequilibrium in the course of an epileptic aura in a proved case of glioma of the right temporal lobe: "Rushing sensation in the left ear, head swims." During this stage "speech wrong, talking from one side of my mouth." This is followed by pins and needles in the left hand.

(2) When the aura, in addition to sensation of movement and tinnitus, comprises other features such as visual and olfactory hallucinations, depersonalization, etc., temporal lobe epilepsy is the more likely diagnosis.

(3) Focal post-ictal symptoms are of course not uncommon in epilepsy in association with intracranial tumours. The post-ictal symptoms in the latter cases, if not permanent, are, however, apt to be more enduring than in cases of vestibular epilepsy included in Group A.

(4) Inter-ictal labyrinthine disturbances, especially when the latter can be provoked by sudden movements of the head, suggest vestibular epilepsy.

Vestibular vertigo is not infrequently conjoined with a variety of other symptoms, which may render the differential diagnosis between "epileptic vertigo" and vestibular epilepsy difficult. "Vertigo, with reeling, is only one-half of the patient's condition. We may call these two symptoms, locomotor symptoms. The following additional symptoms we may call 'vital.' We see that the patient is pale and haggard, that there is profuse perspiration. He tells us that he feels sick, and he may vomit. He has horrible depression, he may say that he feels as if he were going to die. Another symptom is pain in the head" (Jackson, 1880). Taking the last point first, a severe localized headache may be consistently one of the first symptoms of an attack. In some individuals there is one further important relevant "vital" symptom of vertigo. This is diplopia which usually appears concurrently with and endures as long as the vertigo, irrespective of whether the latter arises spontaneously or is produced by caloric testing. Diplopia is usually of horizontal type, but may also be vertical and resemble the vertical diplopia also arising with vertigo, and caused by skew deviation (Russell Brain, Daniel, and Greenfield, 1951).

Diagnostic difficulties arise when there is a failure to recognize the presence of a vestibular disorder, either because of the absence of demonstrable labyrinthine abnormalities or because interictal disturbances are slight or, if severe, true vertigo is lacking. In these latter cases an enquiry can only elicit from the patient a vague account of a sudden, often profound inability to orientate the position of the body in

relation to the surroundings, and a frantic effort to overcome this by grasping anything within reach. There is no sensation of movement but the usual "vital" symptoms of vertigo are present and locomotion is disturbed.

Psychoneurotic disturbances may occupy the central position in the clinical picture, and thus mask the vestibular origin of the psychoneurotic reaction which may include overbreathing tetany. A feeling of instability, often continuous for long periods, may add further difficulty in the diagnosis. This sensation is variously described by patients as "a dazed feeling," "continuous feeling of to and fro," "rocking movement." Owing to loss of stability surrounding objects seem to lack the property of solidity; there is a tightening pressure in the head—"head is not clear"—"head is thick"—"stomach is out of sorts"—all this is attended by a "horrible depression" mentioned by Hughlings Jackson. A characteristic feature is that these sensations are minimal when the subject is at rest and are aggravated by movements, not only of the subject but also of the surrounding objects, e.g. traffic, moving machinery, movements of rivers or sea, etc. This symptom complex, which has received little attention in the literature, is not associated with any obvious disturbance of locomotion, it is reminiscent of Hitzig's (1874) "first degree of galvanic giddiness" elicited with a minimal current.

Very rarely a similar syndrome is met with in association with tumours of the temporal lobe, as described by Penfield and Jasper (1954) (Case M.Bu). They regarded it as an epileptic phenomenon and felt justified in classifying it as epilepsia partialis continua.

In the course of vertiginors attacks of vestibular origin disturbance of consciousness is a not infrequent occurrence, and apart from vestibular epilepsy these cases fall broadly speaking into three main classes which have to be differentiated from vestibular epilepsy :

(1) *Vaso-vagal Syncope of Lewis provoked by Vertigo*

The mechanism involved in the loss of consciousness would appear to be simply an acute fall in the blood pressure brought about by peripheral vasodilatation, mainly of arterioles of muscles. Symptoms which the patient had perhaps experienced in the past in the course of an ordinary faint make their appearance after vertigo has been present for some time, and loss of consciousness is as a rule gradual ("bradyapsychia") (Campbell, 1950). Various transient disturbances of vision as also impairment of hearing and vertigo are the common parodromata of the simple faint (Case 9) (Behrman, 1951).

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Special scrutiny is required to decide whether deafness, tinnitus, or vertigo preceding a faint are to be regarded as elements of the syncope symptom-complex or of some labyrinthine disturbance engendering syncope. The early onset in the attack, duration and severity of vertigo before loss of consciousness, and especially its presence after consciousness is recovered, are points of assistance in the differential diagnosis.

(2) *Overbreathing Tetany*

In some patients, vertigo leads to over-ventilation and consciousness is lost as a result of overbreathing tetany.

(3) *Concussion*

The falls consequent upon vertigo may result in concussion with perhaps retrograde amnesia long enough to include the period of vertigo which may have preceded the fall.

Mechanism

Hughlings Jackson quotes with approval Moxon's dictum: "You must know diseases as a hunter knows his lions and tigers." The object of this communication is to draw attention to the syndrome of vestibular epilepsy and lay down criteria for its recognition. Since the purely clinical approach adopted here does not permit the formulation of definite views regarding underlying physiopathological mechanism, only a brief discussion of some of the possible factors will be made. If vestibular epilepsy is indeed provoked by focal proxysmal overactivity of the vestibular system as previously defined, it must be regarded as a sub-group of epilepsies having a sensory precipitation. The factors which favour the occurrence of this form of epilepsy may be presumed to apply also to vestibular epilepsy, and a brief analysis of them may be pertinent.

(1) *Cortical Lesion*

Hughlings Jackson (1886) in one of his prophetic footnotes says: "I think it very likely that every patient subject to fits of any class has an epileptogenous zone—that disturbance of the part of the periphery most especially represented in the 'discharging lesion' may provoke a fit." He described only a few cases showing definite sensory precipitation of fits. Nevertheless he surmised, as would appear from this remark, that far from being rare, sensory precipitation of fits was a universal feature of all forms of epilepsy, though the facility with which such precipitation could be effected was variable. Furthermore, he assumed that the situation of the epileptogenous zone was strictly related to the situation of the "discharging (epileptogenic) lesion." This

relationship has been confirmed clinically by Gordon Holmes (1927), who observed when studying disturbances of sensation produced by cortical lesions that a seizure sometimes occurred when the affected part was being examined. In none of the electroencephalograms in this series of vestibular epilepsy was it possible to demonstrate a definite focal cerebral abnormality, though this, of course, does not entirely negative the presence of a focal cerebral lesion.

(2) *Abnormality of Peripheral Afferent Pathways*

In none of the cases in which caloric vestibular stimulation has been carried out in this series were fits provoked, and no notable hyperexcitability was demonstrated.

(3) *Startle Facilitation*

In the case-notes of the patient with sensory precipitation of fits, Hughlings Jackson mentions that "touching any part of either side of his head or face would bring on the attacks . . . A fit would not occur if he knew he was going to be touched." Surprise as a factor enhancing the effectiveness of sensory stimuli in precipitating epilepsy has been noted by many others. The instantaneous manner of onset of paroxysms of vertigo of vestibular origin may, therefore, be a factor and it may not be without significance, as has already been mentioned, that vestibular epilepsy occurred either immediately after the commencement of a vestibular paroxysm or not at all.

(4) *Cortical "Activation" by Centripetal Impulses*

Gerebtzoff (1940) working in 1939 in Bremer's laboratory in Brussels utilized the l'encephale isole preparation (section below medulla oblongata) in his studies of the cortical projections of the labyrinth. He noted an immediate change in the resting pattern of the elecro-corticogram on rotational and caloric stimulations of the labyrinth and on faradic stimulation of the acoustic nerve. The change was characterized by greatly increased frequency and amplitude of electrical cortical activity. While maximal in what he regarded the labyrinthine projection areas, these changes could also be demonstrated in every accessible cortical region. Excision or "isolation" of the labyrinthine projection areas did not modify this generalized cortical effect. Thus the cortigram typical of the peaceful wakefulness of the "encephale isole" upon labyrinthine stimulation showed changes which Bremer (1935) had a few years earlier recognized as occurring on arousal from sleep. These considerations, as also experiments involving the division of vestibular pathways at different levels, led Gerebtzoff to postulate the

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existence of collaterals of lemniscal fibres, collaterals which excited a subcortical "centre de l'eveil." Neurophysiological research since 1940 has demonstrated that not only vestibular afferent impulses but all forms of centripetal impulses, as also those provoked by stimulation of chemoreceptors of the carotid body and baroceptors of the carotid sinus, produce this generalized cortical excitation (Lewy and Gammon, 1940; Lindsley *et al.*, 1950; Koella and Gellhorn, 1954; Gellhorn *et al.*, 1942). Thus on application of a nociceptor stimulus, e.g. immersion of hind-leg in water at 55°–65° C. for several seconds, strychnine spikes increase in frequency in all cortical areas. The responsiveness of the auditory and visual projection areas is increased to acoustic and optic stimuli respectively if the latter are combined with the above mentioned nociceptor stimulus (Gellhorn, Koella, and Ballin, 1954). These authors believe that this increased reactivity is brought about by interaction at the cortical level between the sensory volleys and activation evoked by the arousal reaction. They have also shown that as a result of this interaction, the reactivity of a convulsive focus to specific projection impulses is increased and also the spread of convulsive activity is favoured. Gellhorn and Ballin's (1948*b*) study of cortical potentials in cats subjected to intravenous injections of picrotoxin showed that on nociceptor stimulation (ligation of sciatic nerve) though there was generalized cortical activation, various cortical areas reacted differently. There was increase in spikes (hypersynchronization of neuronal activity) in some areas and diminution of spikes (asynchrony) in others. They interpreted these differences being due to greater recruitment in cortical regions which are in a state of higher excitability. They argued that despite a tendency to asynchrony this greater recruitment on afferent stimulation might lead to intensification of convulsive discharges. They also found that the degree of recruitment is greatest in the specific cortical projection area and also depends on the intensity of the stimulus. (Gellhorn and Ballin, 1948*a* and *b*). The available evidence suggests that sensory stimuli differ quantitatively in their ability to produce cortical activation under experimental conditions. This characteristic is shown in decreasing order by different modalities as follows: pain, chemoceptor stimulation with CO_2, proprioception, hearing, and vision. (Bernhaut, Gellhorn, and Rasmussen, 1953). On analysis of this series it is evident that the effectiveness of the various afferent stimuli to bring about cortical activations is paralleled also by their effectiveness in arousing autonomic reactions ("vital symptoms"). It is significant, therefore, that Gellhorn and Ballin (1948*b*) should have found that under experimental conditions, on nociceptor stimulation cortical

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activation only occurred when the intensity of stimulation was adequate to elicit pain reflexes, i.e. autonomic activity (e.g. dilatation of pupils, increased rate of respiration, etc.).

The experiments of Gerebtzoff would indicate that vestibular impulses have an ascendant position in this series, for as Gerebtzoff says: "Le chat, qui s'est endormi sur la branche d'un arbre et qui glisse peu a peu et tombe, n'est averti de son glissement ou de sa chute que par son labyrinthe. S'il continuait a sommeiller, il s'ecraserait sur le sol."

Recent neurophysiological advances suggest, therefore, that if afferent stimulation were to set up epileptiform cortical activity, the location of the latter would be partly determined by the nature of the stimulus employed and by the pattern of resting cortical activity. The degree of cortical activation by a given stimulus and, therefore, the facility with which such epileptiform activity would be elicited seems to be paralleled by the autonomic activity which this stimulus will also engender. However, many factors favouring the disposition to increasing synchronization and, therefore, to convulsive discharges on afferent stimulation are still unknown. Even under experimental conditions, as has already been mentioned, there are differences in degree of convulsive response to a given stimulus, though all parts of the cortex are in a similar state of picrotoxinization, the drug having been administered intravenously. Some of these as yet not fully understood factors which influence the response to sensory stimulation of groups of neurones outside the specific projection areas must be invoked to account for the occasional epileptic response in a few individuals to vestibular stimulation. Williams (1950), commenting on the high proportion of uniovular twins showing identical EEG, observes that "in the present search for epileptic foci there is a great tendency to forget the importance of the constitutional factor." The significance of this factor emerges clearly in such cases of vestibular epilepsy as 2 and 5, in which there is a previous history of epilepsy and/or a family history of epilepsy. Thus considered, vestibular epilepsy is but one example of a large group of sensorily precipitated epilepsy—i.e. epilepsy provoked under certain circumstances in some individuals by the stimulation of various types of receptors, e.g. baroreceptors, sonoreceptors, nociceptors, etc. (Behrman, in preparation). Thus, for instance, stimulation of baroreceptors of the carotid sinus will cause intensification of reappearance of chemically induced convulsions (Gellhorn *et al.*, 1942).

Electroencephalographic findings in Vestibular Epilepsy

It was not found possible to induce vestibular epilepsy by caloric stimulation, and no EEG records were therefore obtained during a

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seizure of vestibular epilepsy, but the theoretical considerations previously adduced would lead one to expect that such records would resemble the records of induced attacks of carotid sinus syncope of "cerebral type," i.e. without associated cardiac or peripheral circulatory disturbances. Romano *et al.* (1940) and Forster *et al.* (1942) noted that the characteristic EEG feature of these attacks was greatly increased fast beta activity. Forster *et al.* in fact speak of demonstrable "direct cortical accelerator effect of sinus stimulation . . . In some of the cases (the acceleration) is comparable to that which occurs at the onset of *grand mal* epileptic seizure."

It would be an oversimplification to assume that desynchronization would be the only effect of the arousal mechanism on the EEG. Li, Jasper and Henderson (1952) have also observed precisely the opposite type of change in some cases, and Engel *et al.* (1944) have reported diffuse slow wave pattern as the most prominent feature in a case of carotid sinus epilepsy. These observations in man are in line with experimental conclusions of Gellhorn and Ballin (1948*a*, and *b*) previously mentioned. Arduni *et al.* (1952) studied the effect of stimulation of bulbar reticular formation, as also of stimulation of various receptors on topically produced strychnine "spikes," and obtained both desynchronization and epileptic EEG responses depending on the "excitability of the preparation." Lairy-Bounes *et al.* (1952) also found convulsive activity in areas of strychninization even when these were outside the specific projection areas of the stimulated sensory pathways. The change in the EEG produced by the arousal reaction would appear to depend on a rise of cortical excitability, the degree and distribution of which is modified by a number of secondary factors.

A total of 13 resting EEG records were available for analysis. 7 records were classed as normal and 6 records as "epileptic," mainly because on hyperventilation they showed paroxysmal bilateral activity of mixed frequencies, often in all leads. One patient's first record was normal; the second record about nine months later was epileptic.

Therapy

Broadly speaking, two main factors are concerned in the causation of vestibular epilepsy:

(1) "Occasional, sudden excessive discharge" of the vestibular apparatus.

(2) Rise of cortical excitability evoked by the discharge. The mechanism whereby as a result of this change a seizure is initiated remains obscure.

Treatment has been directed towards controlling both factors as far as possible. In one case in view of loss of useful hearing in one ear, alcohol injection of the corresponding labyrinth was performed. After the effect of unilateral labyrinthine paresis had worn off, the patient has remained free from fits for the past twelve months. Anti-convulsants were made use of to suppress seizure manifestations. Spontaneous remission of idiopathic labyrinthine affections is, of course, commonplace and this must be born in mind in assessing the value of treatment.

Summary

(1) A number of cases are described showing a recurrent transient post-epileptic vertiginous state.

(2) Arguments are advanced suggesting that this syndrome is a variant of vestibular epilepsy, i.e. a form of epilepsy in which seizures are provoked by excessive, spontaneously arising discharge of the vestibular apparatus.

(3) Evidence is also adduced indicating that vestibular epilepsy is a sub-group of sensorily precipitated epilepsy, i.e. epilepsy provoked under certain circumstances in constitutionally predisposed individuals by the stimulation of various types of receptors.

(4) Paroxysmal vertigo of labyrinthine origin is the most frequent cause of vestibular epilepsy.

(5) A classification of vestibular epilepsy is suggested and the clinical features, differential diagnosis and therapy are discussed.

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RESIDUAL FUNCTION FOLLOWING HEMISPHERECTOMY FOR TUMOUR AND FOR INFANTILE HEMIPLEGIA

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CEREBRAL hemispherectomy, from its first application by Dandy (1928) until the past few years, has been a radical procedure used only in patients with infiltrating gliomas. Krynauw (1950) aroused new interest in the procedure by demonstrating that young patients with infantile hemiplegia associated with uncontrollable convulsions, athetosis, tantrums, and mental deficiency, could be greatly benefited by removal of the hypoplastic or atrophied hemisphere.

In the past twenty-three years we have performed cerebral hemispherectomy on 10 patients who had gliomas and, with perhaps 1 exception, each has been left with some intellectual impairment in addition to the serious physical defect. The improvement in intellectual and physical functioning which has followed the operation in patients having infantile hemiplegia prompted the authors to compare the post-operative state of these latter cases with the residuals in our patients who had the operation for brain tumour. Of these 10 patients who underwent hemispherectomy for glioma, 1 died of hyperthermia within thirty-six hours; 1 died of post-operative meningitis within four weeks; 1 patient survived post-operatively for six months but remained in a vegetative state. The remaining 7 patients survived for periods of one to seventeen years after operation; 3 of them died of recurrence, 1 following a head injury, and 3 still are living. 8 of these 10 patients were subject to convulsions before operation, and none of them had seizures afterwards. Six patients were available for adequate post-operative testing.

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Surgical Technique

The technique of hemispherectomy can be performed more readily with the patient in the sitting or semi-reclining position. With the employment of a large bone flap, the hemisphere may be removed in one piece with very small loss of blood. In operation for glioma, the line of incision should be close to the mid-line but we have usually spared the hippocampal gyrus, the head of the caudate nucleus, and the greater portion of the thalamus and subthalamic structures. The middle cerebral artery is divided just beyond the carotid bifurcation and the anterior cerebral artery distal to the anterior communicating. This method spares the circle of Willis and ensures more adequate circulation to the remaining cerebral tissue.

Before advising hemispherectomy for glioma, the social and economic aspects in each case received careful consideration. Our experience indicates that the operation should be restricted to cases of slowly growing gliomas in or near the central fissure of the right hemisphere of right-handed patients. The possibility of cure of a glioma of the temporal lobe by any procedure is very remote and the period of useful survival that follows removal of frontal and occipital lobe tumours by lobectomy contra-indicates the more radical operation in these cases.

Post-operative Results Reported in Cases of Infantile Hemiplegia

Krynauw (1950) operated on 12 patients who had infantile hemiplegia. In none of them did hemispherectomy cause more than a transient increase in the existing hemiparesis and, with the passage of time, some of the patients actually developed more power in the paralysed side than they had before the operation. In addition, there was a considerable lessening of the spastic athetosis. The initial profound loss of all cortical sensory modalities was subsequently reduced, and quantitative and qualitative appreciation of pain and tactile sensation returned to nearly normal. There was some impairment of position sense, particularly in the fingers, and a raised threshold for 2-point discrimination, about three times the normal level. The previously marked dysrhythmia evident on the electro-encephalogram of the intact hemisphere, was reduced after operation.

Cairns and Davidson (1951) reported their experience with 3 similar cases. They agreed with Krynauw that either cerebral hemisphere may be removed without causing an increase in speech difficulty in

patients having infantile hemiplegia. They left intact the thalamus and caudate nucleus and preserved the arteries to the basal ganglia. They did not remove the hippocampus, because of its connexion with the hypothalamus. In their cases, the range of voluntary movements was not decreased, but modalities of sensation lost on the affected side in the 2 patients old enough to be tested, were not restored by operation. The patients were happier and more useful to themselves as a result of the procedure. Cairns and Davidson concluded that the results of hemispherectomy for infantile hemiplegia showed that after the onset of the disease, control of contralateral limbs passes from the diseased hemisphere to other parts of the brain.

Alcalde (1951) reported his experience in 4 similar cases. In the 3 patients who survived the immediately post-operative period, he noted no increase in the motor deficit, in spasticity, or in abnormal reflexes. Sensation and visual fields could be tested only in his oldest patient. All were improved psychologically. Convulsions were controlled without medication. There was no lasting speech change regardless of whether the right or left cerebral hemisphere was removed, indicating that the intact hemisphere was dominant for speech in each instance.

Gros and Vlahovitch (1951) reported 2 cases of infantile hemiplegia treated by hemispherectomy. They believe that the ability to walk is due to the retention of the head of the caudate nucleus, and that the remaining gross movements of the hemiplegic side are attributable to the ipsilateral, secondary, motor, cortical centres in the dorsal lip of the sylvian fissure and in the medial frontal cortex. Post-operatively, they found that fine movements were abolished, that deep and superficial perception of pain and localization of touch and pain were relatively preserved and that epicritic and gnostic sensibilities were abolished except in the area of the trigeminal nerve.

McKissock (1953) reported the results of hemispherectomy in 18 patients with infantile hemiplegia. Each of these patients had epilepsy, temper tantrums, and mental retardation. 12 of the patients were completely relieved of their convulsions and 14 were relieved of their temper tantrums. One patient died. In 12, the hemiplegia was unchanged; in 2 it was worse; and in 3 it was improved. In 3, the mental state was unchanged; in 1 it was worse; and in 13 it was improved. McKissock afforded one of us (W. J. G.) an opportunity of examining 2 of these patients. The paralysis and spasticity of the arm and leg were much less pronounced than in our patients in whom the cerebral hemisphere had been removed for glioma. There were movements in the thumb and a quite useful hand. There was partial loss of sense of

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position and partial but certainly not complete astereognosis. Two-point discrimination was fairly good. There was no extinction when stimuli were applied simultaneously to corresponding areas on the two sides. Bates (1953) subsequently reported that movements of the hemiplegic limbs in these cases were elicited by electrical stimulation of the exposed mesial surface of the remaining hemisphere after the diseased hemisphere had been removed.

Fleischhacker (1954), who described in considerable detail the findings in 5 of the cases of infantile spastic hemiplegia operated on by McKissock, emphasized benefits such as improvements in general disposition and behaviour, and the drastic reduction in frequency of convulsions. He reported improvement in gnostic sense and motor abilities in the spastic hand in 3 of the patients. He found no disturbances in recognition of body scheme or body image such as that which frequently has been pointed out by Nielsen (1947) in adult patients having vascular degeneration of the brain.

Uecker, French and Johnson (1954) made systematic psychological studies of 7 cases of infantile hemiplegia before and after hemispherectomy. Improved adjustment was noted in 5 patients. None of the subjects fell below the pre-operative level in intellectual functioning and some improvement was probable in 2 cases, although this could be attributed to withdrawal of anticonvulsant drugs.

French and Johnson (1955) studied the effects of cerebral hemispherectomy on the motor function of 8 patients with seizures and hemiparesis developing at an early age in life. No permanent further deficit in motor capacity developed even when the caudate nucleus and the hippocampal gyrus were included in the resection. They believe that the preservation of motor function is due entirely to the intact hemisphere having assumed the function of the pathologic side many years pre-operatively, and that the defective hemisphere actually offers only a restraining influence on the motor functions of the normal side.

To this review of previously described cases we would like to add 1 case from our personal experience. This was a woman of 29 with an infantile left hemiplegia and uncontrollable generalized tonic seizures which had begun at the age of 5 years. The patient had been delivered prematurely by Cæsarean section, the birth-weight was $4\frac{1}{2}$ pounds and she was given oxygen for several days after birth. When she was 5 months old, a physician told the mother that the child was hemiplegic. From this story it appears likely that the right cerebral hemisphere was defective at birth. During the surgical removal of this hemisphere, it was observed that no convulsive movements were pro-

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duced when the region of the internal capsule was divided with the electrocautery. This was contrary to our experience with cases of brain tumour and was believed to indicate the absence of functioning motor fibres in the internal capsule. The removed specimen included all of the cortex with the exception of a small area of the mesial frontal cortex below the anterior genu. Basal ganglia were not demonstrable in the removed specimen which weighed only 245 grammes and contained a large porencephalic cyst in its mid-portion.

Prior to operation the patient was confined to bed and was obtunded by frequent seizures and large doses of anticonvulsants. Grasp in the left hand was extremely feeble and she was unable to identify any object placed in it. The verbal scale of the Wechsler-Bellevue Form 1 revealed an I.Q. of 67. Thirty-seven days after operation, the verbal scale I.Q. was 78. This improvement was believed to be due to relief from seizures and drastic reduction in anticonvulsant medication.

Six months after operation she was free of seizures without medication. She walked with a barely perceptible limp. The left arm was semiflexed at the elbow and acutely flexed at the wrist. There was a claw hand with the proximal phalanges in extension, the distal phalanges in flexion. Movement of the thumb consisted of little more than a slight ataxic tremor. There was only very slight flexion and extension of the fingers on command. Motion in the upper extremity, therefore, was about the same as prior to operation.

Sense of position was accurate at the shoulder, elbow, and wrist. She could not identify the position of the thumb, but she could tell when the remaining digits were passively flexed or extended, provided they were all moved at the same time. A light touch was always identified and correctly localized on the thumb and little finger, usually on the index finger, and occasionally on the third and fourth digits. Cool and tepid temperatures were correctly distinguished on ten consecutive testings and were felt to be of the same temperature as in the normal hand. Pinprick was appreciated to be of the same quality and intensity in the left hand as in the right. There was, however, almost complete loss of 2-point discrimination in the left hand—that is, when touched with two fingers at a distance of 3 in. apart, she would call it "two" 60 per cent of the time and "one" 40 per cent of the time. When the left hand and the left side of the face were touched simultaneously, there was extinction of the stimulus in the hand—that is, the face-hand test was positive for organic brain defect.

The patient was able to identify some objects placed in the left hand. Since she was unable to manipulate the object herself, it was observed

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that her responses were more accurate when the object was moved in the hand by the examiner. She could invariably tell when there was nothing in the hand. Two of the examiner's fingers, whether still or moving, were invariably identified as "your finger." When the object was small and not moving, or when it was one of the examiner's fingers and not moving, she could seldom tell there was anything in her hand. This patient therefore had considerably more function in the hemiplegic side than was observed in our tumour cases described below.

Comparison of Results

In order to make a systematic comparison of the residuals following hemispherectomy for brain tumour with those following the operation for spastic hemiplegia, the data are presented in four categories of cerebral function, namely: motor, sensory, language and psychologic.

Comparison of Motor Changes

Motor changes in patients with brain tumour.—Of the 7 patients who recovered from the immediate hazards of the operation for brain tumour, each regained sufficient power in the leg to enable him to walk without aid. In the adults, the gait was typically that of a spastic hemiplegia with no voluntary power to activate the toes or to manipulate the ankle-joint. Voluntary control of the wrist was absent and only 1 or 2 adults in the brain-tumour group seemed able to increase the spastic flexion of the fingers on command. In no case was there movement of the thumb or a useful grasp. The 2 adolescents in this group showed a greater freedom of global movements in the extremities and each had some voluntary control of the wrist and ankle joints. What motor capacities in the paralysed limbs were retained, appeared within a matter of hours or weeks following the operation, after which none of these patients developed any additional skill or motor increment on the hemiplegic side.

There was a central facial palsy that was relatively slight in the adults, but for some reason was more pronounced in the 2 adolescents. The tongue showed no deviation from the mid-line when protruded. In none of these patients was there evidence of impairment of axial muscles and none showed signs of visceral or autonomic defect.

Motor changes in patients with spastic hemiplegia.—In patients with infantile spastic hemiplegia it must be pointed out that none of them in the pre-operative phase presents a complete hemiparalysis of the classic form seen in subjects with an acquired lesion due to apoplexy.

They are young people who through their developmental years and by unknown ontogenetic forces have grown up with a mono-hemispheric brain. The outstanding feature in these patients is a greater mobility of the shoulder and elbow joint, sometimes as powerful and complete a function as exists in a normal person. Moreover one rarely finds the completely spastic claw-hand of the typical elderly person with hemiplegia. There is usually some capacity to manipulate the thumb in adduction movement and a feeble flexion and extension of the fingers as well as of the wrist. Hence the patient has some primitive grasping and praxic control of the hand with ability to perform crude manual activities. In the lower limb the walking action is typical of spastic hemiplegia but there is often in addition some capacity to flex and extend the ankle-joint and to move the toes in plantar flexion.

None of these functions is lost in spastic hemiplegic patients after hemispherectomy. After a temporary flaccid weakness, they quickly reappear and in some instances are enhanced following the operative procedure. Above all benefits is the freedom from convulsive seizures in the paralysed limbs which may well be the one factor which promotes the improvement in muscle strength and in motor co-ordination. As French and Johnson (1955) have pointed out, this improvement occurs even if the caudate nucleus and the entire mesial portion of the temporal lobe are included in the hemispherectomy.

Comparison of Sensory Defects

Sensation in patients with brain tumour.—Testing sensory function in the patients who had been operated upon for brain tumour was a frustrating experience both for the examiner and for the subject. The patient found it difficult to concentrate on the testing when the paretic side was being checked and all patients exhibited rapid fatigue with accompanying inattentiveness and unreliability of response. In the adolescents, responses on the whole indicated more sensory cortical function than in the adults, but in some examinations the responses were not any better.

In general there is a delay in appreciation of all stimuli on the paralysed side. This delay is quite short in the trigeminal area and longest in the distal portion of the extremities. Sense of position is fairly well preserved at the hip, perhaps less so at the shoulder, poorly at the knee and even more poorly at the elbow. It is lost below the elbow and the knee. There is, of course, complete astereognosis. In the affected trigeminal area light touch, cool and tepid temperatures are appreciated only slightly less accurately than on the normal side, but

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below the face these modalities are not recognized at all. Pressure with the examiner's fingers or a sharp point shows progressively greater impairment of appreciation and localization of the stimulus in the following order : face, trunk, thigh, upper arm, leg, forearm, foot and finally the hand. In the same areas two-point discrimination shows a corresponding degree of impairment. A pain stimulus on the affected side is consistently more disagreeable than on the normal side. Cold and hot stimuli are painful and cannot be differentiated. Pressure stimuli, applied simultaneously to the face and to an area below the face usually are appreciated only in the face. Pressure with a finger or with a pin applied simultaneously to the two sides in similar areas always is appreciated on the paretic side in the trigeminal area and nearly always on the trunk, thigh, leg, and upper arm. There is extinction of the stimulus below the elbow and below the knee on the paretic side.

In these brain tumour cases, therefore, it may be said that, *with the exception of the face,* the loss of motor and sensory function is proportional to the surface area of cortical representation.

Sensation in patients with spastic hemiplegia.—In the patients with infantile hemiplegia the sensory changes after hemispherectomy were equally difficult to evaluate. What defects were found may have largely existed before the operation because recent studies made by Tizard, Paine and Crothers (1954) report that more than 50 per cent of 106 persons having spastic hemiplegia acquired at birth or soon thereafter, who had not been operated upon, had some type of sensory impairment on the affected side. Most frequently the defect consisted of total or partial astereognosis or diminished two-point discrimination.

In the trigeminal area after operation, all modalities of sensation are normally perceived. Below this area, two-point discrimination, appreciation and accurate localization of pin-prick, touch, and pressure were better retained in the spastic hemiplegic person than in tumour cases. The poorest results were found to be in the arm distal to the elbow and particularly in the thumb and first two fingers. However, and this is a matter of great significance, in some cases there was retention of some degree of stereognosis and sense of position in the digits, preservation of epicritic sensibility and lack of distortion of painful stimuli. This was not true in any of our tumour patients.

A striking and constant finding in both groups of patients was the retention of all modalities of sensation in the trigeminal area. We believe that the large bilateral cortical representation of the face in man may be a phylogenetic carry-over from lower mammals which, not

having developed a hand, are largely dependent on snout sensation to examine and to "manipulate" objects in their environment.

Comparison of Language Disturbances

Speech disturbances in patients with brain tumour.—Following hemispherectomy for brain tumour, language disorders were not serious unless the left or dominant hemisphere was resected. Experience with the operation has shown that handedness is not always a safe indication of the side of the brain that carries the major part of language function. This was demonstrated in the 17-year survivor of our series (Case 4) who, though left-handed, suffered no speech deficit after removal of the right hemisphere and only a temporary dyscalculia. It was demonstrated conversely by the case of the left-handed adolescent (Case 7) who exhibited a persistent alexia and anomia following removal of the left hemisphere.

Humphrey and Zangwill (1952) studied dysphasia in left-handed patients with unilateral brain lesions. Five of their patients had right- and 5 left-hemisphere lesions. They found that all 5 patients with left-hemisphere lesions had some degree of dysphasia, and in 1 it was disabling. In the 5 with right-hemisphere lesions, 4 had dysphasia. They found that calculation was permanently impaired in 4 of the 5 with right-hemisphere lesions. If dyscalculia is excluded, the incidence of dysphasia and other symptoms was consistently higher in the group with left-hemisphere lesions despite the left-handedness. Their findings support the hypothesis that cerebral dominance either does not occur in so-called left-handed persons or if it does, it is less well developed than in right-handed persons.

In right-handed persons, a resection of the left hemisphere is certain to impair speech function in varying degrees. However, where speech engrams have not become firmly established in the left hemisphere, as obtains in young people or in patients having spastic right hemiplegia acquired at birth, a left hemispherectomy may not cause any disaster to speech.

Hillier (1954) reported an experience with a left hemispherectomy for tumour after presenting a survey of the literature, which comprised only 4 previous cases including the often-quoted report by Zollinger (1935). Hillier's patient was a 14-year-old boy with a malignant glioblastoma. After several partial resections and subsequent complications with infection, a total left hemispherectomy was done. The boy was right-handed. Twenty-seven months after the operation, comprehension of the spoken word was quite accurate. He was capable

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TABLE.—RESULTS OF HEMISPHERECTOMY FOR GLIOMA

Case No. Sex and Age	*Handedness and diagnosis*	*Intellectual functioning*	*Post-operative course*
1* F 31 years	Right-handed Oligoglioma, right sylvian fissure	Members of patient's family greatly impressed by her relative recovery, and loath to admit any defect. None the less, they humoured her in every way possible, carefully avoided direct criticism of her behaviour, and lauded her greatly for any minor accomplishment. She was never asked to assume a great deal of responsibility in managing such things as the budget, or in initiating any new programme involving the various members of the family. She was never asked to make any major decisions. The family admitted that she was easily brought to tears, was occasionally maudlin, and abnormally elated. She wrote a good letter but was inclined to repeat herself without being aware of it. The attitude of the family clearly showed that they appreciated an innate deficiency but were not willing to admit it openly. Overtures on the part of a psychiatrist to probe into her mental processes were bluntly discouraged	The patient got around quite well without aid. She went up and down stairs unassisted, carried out the simpler household chores, and shopped for the household. Well for 4 years and 3 months after her operation at which time she fell down the cellar stairs. Following this she was operated upon for a subdural hæmatoma, then showed gradual mental and physical deterioration, and died 4½ years after hemispherectomy. Post-mortem examination not obtained
2 F 35 years	Right-handed Astrocytoma, right internal capsule	Did not regain consciousness	Died of hyperthermia 36 hours after operation
3† F 25 years	Right-handed Astrocytoma, right temporal lobe	Too sick for adequate testing	Died of *Staph. albus* meningitis 27 days after operation. No evidence of tumour at post-mortem examination

4‡ M 35 years	Left-handed Astrocytoma, right motor area	For a year or more his arithmetic was quite poor but he later regained his former performance level. He spends money foolishly and seems unable to plan for the future. 15 years after operation – I.Q. Wechsler-Bellevue Scale: 96. Wechsler Memory Scale : 89. Rorschach showed some determinants characteristic of brain damage. There was paucity of associations, stereotypy and some perseveration of ideas. Tests indicated a person of average intelligence but with a superficial mentation with little originality, lacking in any deep introversive processes and in motivation, and given to sudden and illogical mood swings and easy petulance	Patient was quite helpless early in post-op. course due to loss of function of the dominant hand. He gradually improved the dexterity of right hand, and with the passage of time he became able to write. His wife took over the management of his restaurant. He goes on camping trips with his cronies. He enjoys meeting people and telling stories, some of which are embarrassing to his wife This patient is living 17 years after his operation. He does everything for himself except tying his shoelaces, but is of little help to his wife in his business
5§ M 27 years	Right-handed Astrocytoma, right temporal lobe	Follow-up examination 14 months after operation : Superficially smart and clever in repartee. He is emotionally unstable, inconsistent and lacking in perseverance. Careless of his personal appearance. Not greatly disturbed by his physical handicap. Has great ambitions but is unable to carry out a consistent programme for making a living	Patient was able to assist with simple chores about the farm, which he could accomplish with one hand. The left arm was flaccid and dangled at his side. He did not attempt to resume his former occupation as a bookkeeper. This patient died with symptoms of increased intracranial pressure 3 years after operation. Post-mortem examination was not obtained
6 F 26 years	Right-handed Recurrent astrocytoma, right fronto-temporal	Behaviour was " normal " according to mother. Did not return for follow-up examination	Died with symptoms of increased intracranial pressure 1 year after operation. Post-mortem examination not obtained

*This case has been previously reported (Gardner, 1932, 1933, 1954 ; Karnosh and Gardner, 1941 ; O'Brien, 1932).
†This case has been previously reported (Gardner, 1954 ; Karnosh, 1937).
‡This case has been previously reported (Bell and Karnosh, 1949 ; Gardner, 1941, 1954 ; Karnosh and Gardner, 1941).
§This case has been previously reported (Gardner, 1954 ; Karnosh and Gardner, 1941).

(*continued overleaf*)

Case No. Sex and Age	*Handedness and diagnosis*	*Intellectual functioning*	*Post-operative course*
7 F 10 years	Left-handed Recurrent astrocytoma, left frontal	Parents believe she was left-handed from birth. Generalized convulsions began at 3 years. Right Jacksonian seizures began at 9 years, and were accompanied by aphasia. After first operation, which was 1 year prior to hemispherectomy, the seizures recurred but were not accompanied by aphasia. This suggested that encroachment of the tumour on the left frontal lobe may have caused transfer of speech function to the opposite side. Before hemispherectomy, the Stanford-Binet Scale gave her an I.Q. of 72. The Rorschach revealed stereotyped responses, perplexity and perseveration of ideas, all indicative of severe brain damage Following operation she spoke with some hesitation and exhibited some degree of anomia and alexia. A year after operation, the Stanford-Binet Scale was 60. At this time her speech output was more spontaneous but memory function was still defective. 3 years and 11 months after operation, regression was very much in evidence. The I.Q. was 54, the memory quotient was 51, and the Rorschach showed progressive deterioration. No improvement in anomia and alexia	Living. When last examined she was recovering from a Torkildsen procedure necessitated by an obstruction to the escape of cerebrospinal fluid from the cavity. This probably accounts for the regression which was found at last examination. Living 4 years and 5 months post-op.
8 F 9 years	Right-handed Twice recurrent ependymoma, right parietal	Stanford-Binet Scale before operation gave an I.Q. of 97. Examiner believed the score was depressed by a visual defect due to secondary optic atrophy. 2 months after operation, the Stanford-Binet Scale gave an I.Q. of 104. There was a lengthening of attention span though the visual impairment was more severe. Patient appeared depressed and the examiner observed greater mood fluctuation than before operation. 9 months after operation, I.Q. was 98. New learning had taken place and there was a lengthened attention span. 17 months post-op., I.Q. 100. The examiner found not much affect or interest although pleasant and co-operative. Better mental integration shown by less scatter on test. Abstract thinking—poor. Attending sight-saving classes. Grades are B's and C's, formerly made A's	18 months post-op. developed increased intracranial pressure and suicidal ideas. Operation disclosed recurrence on mesial surface of left hemisphere. Died 20 months post-op. Post-mortem examination was not obtained

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C's, formerly made A's

9 M 45 years	Right-handed Thrice, recurrent oligoglioma, right motor area	Before operation, the Wechsler-Bellevue showed a full-scale I.Q. of 118, with a verbal of 122 and a performance scale of 112. 2 months and 13 days after operation, the verbal scale yielded an I.Q. of 113, a loss of 9 points. 3½ years after operation, the verbal scale gave him an I.Q. of 110, indicating an almost static intelligence level. On the memory scale, his quotient was 126. On the Rorschach he gave a minimum number of responses, fatigued easily, displayed a narrow range of associations and little originality or imagination, indicating a dull intellectual functioning, and no ability for deep thinking or for adequate self-evaluation. The affect was that of a rather shallow irritability. The affect at the time of this examination was conditioned by resentment at having been asked to travel 100 miles for testing when he felt well Patient's wife insists that he is " wonderful to live with." She describes him as patient, kind and not at all demanding. He initiates plans for the future, he is interested in the household budget and does not spend money foolishly. She states that her two daughters by a former marriage are very fond of him	Resumed work at a less responsible job 1 year after operation. Has worked steadily and is earning his living 5 years after operation. He does everything for himself except tying his own shoelaces. He has driven a car but feels it is dangerous due to his hemianopsia
10 M 51 years	Right-handed Recurrent oligoglioma, right parietal	Nil. Patient remained in vegetative state probably due to cerebral ischemia, the result of severe arterial hypotension following operation	Living in a decerebrate state 6 months post-op.

of reading individual letters but could not recognize words. He had some anomia and motor aphasia which were rapidly improving.

Speech disturbances in patients with spastic hemiplegia.—In the young patients with infantile right hemiplegia who were subjected to left hemispherectomies, reported in the literature, little is said of speech impairment and it is presumed that adequate language function had been allocated to the intact right hemisphere, or it is just as likely that such elusive impairments as alexia or anomia are masked by the general picture of mental deficiency which is found in many of the victims of congenital spastic hemiplegia.

Comparison of Psychological Alterations

Psychological alterations in patients with brain tumour.—In this area of brain function there exists the greatest contrast between the patients of the two groups after hemispherectomy. With one exception (Case 9) the individuals operated on for brain tumour suffered a loss in terms of personality values. They became dependent, regressive and ineffective people. Systematic psychological tests demonstrate that in most of these subjects intellect *per se* is not the outstanding deficit, for vocabulary and verbalization appear to suffer the least and memory function and recall are not too markedly depreciated. It is in the higher and more complex integrations involving insight, emotional control, initiative, constructive ideation, and imagination that hemispherectomy takes its toll. Beyond this evaluation too many imponderables enter into the problem, for the results of psychological tests show extreme variations between individuals and in the same individual at different times.

Mensh and associates (1952) reviewed the psychiatric phases of 41 cases of cerebral hemispherectomy for brain tumour previously recorded in the literature, and reported their psychological studies of a man who had had the right hemisphere removed in an attempt to cure a glioblastoma. Their conclusions as far as post-operative functionings were concerned did not emphasize anything more specific than did those gleaned from general clinical observations. Investigations of the mental powers after hemispherectomy must be tempered by admonitions such as those mentioned by Goody and McKissock (1951) who remind us that it is important to detach ourselves from the view that there is only one real or true, or standard pattern for cerebral function. There is no one standard brain as there is no one standard person.

Psychological alterations in patients with spastic hemiplegia.—The dramatic relief from epileptic seizures and the general improvement

in emotional control in these subjects have been emphasized by every author who has reported on them. Intensive psychological studies on 7 cases by Uecker and his associates (1954) done before and after hemispherectomy have shown depreciation of intellectual capacity in none of them. What is more gratifying is the observation that in the majority of cases the patient becomes more stable in the emotional spheres, is relieved of temper tantrums, is more capable of attentiveness and he gains in powers of concentration. Moreover in most instances the dulling effects of anticonvulsant drugs are removed, which allows the individual to become more alert and to show more normal interest and initiative. If nothing more, the patient's improved emotional state makes him a more acceptable custodial responsibility.

Summary

A study of patients having brain tumours shows that with one exception, removal of a cerebral hemisphere left the patient with defects in judgment and inability to plan for the future; and in all patients psychometric studies indicated an impairment in insight, in emotional control, in initiative, and in perseverance. The neurological deficit is more devastating than that after similar operations for infantile hemiplegia.

When the functioning of the patients operated upon for brain tumour is compared with that reported in patients operated upon for infantile hemiplegia, it is apparent that, if one hemisphere is impaired, whether by developmental anomaly, birth trauma, or some disease process occurring shortly after birth, other parts of the brain do, to some extent, acquire the functions which otherwise would be performed by the parts that have failed to develop. In the adult nervous system, where physiological centres and pathways and engrams already have been laid down, other areas cannot "take over" the function of parts destroyed. In other words, the immature cortex of one hemisphere can *acquire* functions which nature planned for the cortex of the other side, but (with the possible exception of speech) once a function has become established in the cortex, it cannot be *transferred*. Since corticalization of function is an ontogenetic as well as a phylogenetic phenomenon, the infant can part with his cortex with less resulting functional deficit than can an adult.

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MECHANISMS IN THE PRODUCTION OF HEMIPARESIS ASSOCIATED WITH INTRACRANIAL ANEURYSM

BY

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THE present communication deals with the ways in which hemiparesis is caused by an intracranial aneurysm, and several of these will be illustrated by case reports.

The coincidence of hemiparesis and aneurysm clearly must depend upon the situation of the lesion. Its frequency is suggested by the figures of Richardson and Hyland (1941), who noted 34 examples of hemiplegia among 71 patients who had suffered spontaneous subarachnoid hæmorrhages, most of which presumably were due to aneurysm. Norlén (1952) noted hemiparesis 53 times among 111 cases of aneurysm. By contrast, when the aneurysms were located so as to compress the visual pathways, weakness of the limbs was only rarely observed (Jefferson, 1937). Dandy (1944) reported 14 cases of partial or complete unilateral paralysis of the limbs in his series of 108 aneurysms; 64 of these aneurysms were examples of ruptured lesions and the remaining 44 of unruptured lesions. Only a few of the causes of the paralysis would be common to both groups.

HEMIPARESIS WITH ANEURYSMS WHICH BLEED GROSSLY

Subarachnoid hæmorrhage with compression by extracerebral subarachnoid blood.—No case of local brain involvement by this mechanism has been reported. Dott (1932–33), however, wrote that focal neurological signs could be provoked by extensive subarachnoid effusion, such masses of blood compressing the brain locally rather than disrupting brain substance severely. Dandy (1944) stated that partial and transient hemiparesis was produced by the compression of a motor area by a hæmatoma and the resulting œdema. It is not clear whether he meant extracerebral compression by hæmatoma or intracerebral hæmorrhage.

Intracerebral hæmorrhage.—The association of intracerebral hæmorr-

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hage and bleeding intracranial aneurysm is well recognized. Collier (1931) noted the production of hemiplegia by the rupture of an aneurysm within the brain. Dott (1932–33) also recognized the production of focal signs by blood effusion into the cerebral substance. In the experience of Richardson and Hyland (1941) hemiparesis was the commonest manifestation of intracerebral hæmorrhage into the frontal lobes. Hæmorrhage into the temporal lobe was also associated with hemiparesis. Robertson (1949) in a study of autopsy material found massive intracerebral hæmorrhage present in 56 out of 93 post-mortem examinations. Dandy (1944) noted that if the weakness were complete and followed by little improvement the aneurysm was usually located on the middle cerebral artery. In the series of cases recorded by Richardson and Hyland (1941), lesions which caused frontal and temporal lobe hæmorrhage and hemiparesis were located in the anterior cerebral, anterior communicating and middle cerebral arteries. Although Norlén (1952) did not specify the mechanism by which hemiplegia was produced, in his series of cases the patients with aneurysm of the middle cerebral artery had the highest incidence of associated hemiplegia. He has, however, observed hemiparesis in conjunction with aneurysm in practically every location. Hamby (1952) recorded 25 examples of hemiplegia and 6 of monoplegia among 130 patients suffering spontaneous subarachnoid hæmorrhage. Of those cases studied in the post-mortem room, the cause in most instances was bleeding into the brain substance. Hæmorrhage was found in the frontal lobes, basal ganglia and internal capsule.

Fearnsides (1916) found hemiplegia occurring ten times in 31 cases of autopsied non-embolic aneurysms which had ruptured. He reported lesions in the cerebral cortex and also pathological syndromes of the brain-stem. He concluded that embolic (infective) aneurysms were associated with intracerebral hæmorrhage more frequently than non-embolic lesions.

Case 1.—N. H. A. This 34-year-old housewife noted the unheralded onset of headache, nausea, vomiting and diarrhœa on the morning of August 11, 1954. By noon the patient could not be aroused. She was incontinent and her referring physicians noted a stiff neck and a divergent strabismus. Lumbar puncture disclosed grossly bloody cerebrospinal fluid. The patient slowly improved, became mentally clear and was transferred to the Wadsworth Hospital on the ninth day because of the rapid onset of severe weakness of the left face and extremities and a return of urinary incontinence.

Examination revealed the patient's blood pressure to be 192/130. She was confused, disoriented and incontinent. Movements were absent in the left extremities except for gross proximal joint motion and a left central facial palsy was present. Tone was decreased in these extremities. A left homonymous visual

field defect of uncertain proportions was recorded, as was some sensory impairment on the left side of the body. The plantar responses were bilaterally extensor.

The clinical diagnosis of a rutured aneurysm of the middle cerebral artery on the left was made. The cerebrospinal fluid was pink with 2,650 red cells per cubic millimetre. The patient remained intermittently confused and restless with a consistently elevated blood pressure. Her severe hemiparesis persisted. Following an improved and reasonably alert afternoon she expired abruptly in the evening of August 29, 8 days after admission.

Autopsy examination disclosed the entire right hemisphere to be enlarged, softened and fluctuant. An aneurysm 0·3 cm. in diameter located on the right middle cerebral artery at the origin of its first major branch had ruptured into the substance of the hemisphere causing separation of the temporal and frontal lobes by extensive clot. A tiny second unruptured aneurysm arising from the junction of the left anterior and middle cerebral arteries was also found (fig. 1), Plate XLII.

In this case the mechanism of the production of hemiplegia is not difficult to accept. It is noteworthy that weakness existed in profound degree for nine days before death, part of which time the patient was able to feed herself.

Case 2.—G. M. This 58-year-old man noted weakness and numbness of the right lower extremity eight months before his last hospital admission. Three weeks prior to entry subarachnoid bleeding was diagnosed on the basis of sudden head and neck pain, impairment of consciousness and gross blood in the cerebrospinal fluid.

At the initial examination the patient's blood pressure was 140/90. He was confused and incoherent, and there was weakness in both lower extremities although more marked on the right. When examined four weeks later, seven weeks after his initial bleeding episode, his temperature was 103° F. The patient responded slowly to simple commands. His neck was quite stiff and there was weakness of both the right arm and leg. Bilateral carotid angiography demonstrated a lobulated aneurysm arising from the left anterior cerebral artery (fig. 2). The fundus of the mass tilted across the mid-line. The ipsilateral anterior cerebral artery was attenuated in size while the right (opposite) anterior cerebral artery was displaced to the left. In the post-angiographic state the right-sided weakness was severely aggravated and the patient showed a flaccid hemiplegia. The cerebrospinal fluid was again grossly bloody and under a pressure of 210 mm. of water. The patient expired during the early morning of the day of scheduled operation.

Autopsy examination revealed a thin-walled aneurysm which was surrounded by fresh clot and arising from the left anterior cerebral artery 3 mm. from its junction with the anterior communicating artery. Hæmorrhage had penetrated the mesial aspect of the right frontal lobe and had ruptured into the right lateral ventricle. Extensive intraventricular and subarachnoid blood was present (fig. 3).

Intracerebral hæmorrhage as a cause of the weakness of the limbs is not as well established in this case as in the preceding one. Although the aneurysm was located on the left anterior cerebral artery, it had ruptured into the opposite ventricle, and the intracerebral rupture was on the same side as the major extremity weakness. This aneurysm was so placed as to compress or otherwise involve both anterior cerebral arteries, possibly explaining the bilateral lower extremity weakness

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noted at the time of the initial examination. In this respect it is important to state that at the time of angiography both anterior cerebral arteries were filled with the contrast medium although the filling on the left side was sparse. I mention this because Robertson (1949) has reported an example of obliteration of both anterior cerebral arteries by clot between the cerebral hemispheres in a formalin-fixed specimen, and suggested that during life some changes may have been due to compression of arteries by the aneurysm. Thrombosis of these arteries was not present in the post-mortem examination of this case.

Subdural hæmorrhage.—Collier (1931) commented upon the occurrence of aneurysmal leak into the subdural space with the formation of an organizing hæmatoma. Dott (1932–33) accidentally uncovered a subdural clot of clinical proportion in the course of operating upon an intracranial aneurysm. No mention of hemiplegia as a manifestation was made by him or Collier. Logue (1951), however, found 4 examples of this lesion among 50 cases of ruptured aneurysm and reported a case of hemiplegia in association with the hæmatoma which in turn resulted from aneurysmal rupture. Further experience with the primary association of aneurysm and subdural hæmatoma was reported by Hamby (1952), Bassett and Lemmen (1952) and Clark and Gooddy (1953). It is difficult to ascertain which of several pathological processes may be responsible for the occurrence of hemiplegia when any one alone could be equally culpable. It is probable that subdural hæmatoma is not a major contender for this dubious honour, for even when present the hæmatoma more often manifests itself in other ways.

Embolization from the aneurysmal sac.—Whether such a mechanism is anything more than theoretical is doubtful. Biemond and ter Braak (1933) suggested that a propagated thrombus which forms following rupture might give rise to emboli which would spread into the distribution of the parent vessel of the aneurysm. Dandy (1944) accepted such a possibility as a cause of aneurysm, but no examples were reported. Fiolle (1950) reported a patient who recovered from a traumatic aneurysm of the common carotid artery accompanied by presumed embolization and hemiplegia and Fisher (1954) recorded an example of emboli arising distal to a severely stenosed or occluded cervical carotid artery. I have been able to find no proven examples of such an occurrence in cases of intracranial aneurysm.

Hemiparesis with Aneurysms which have not Bled

Compression of the brain substance by the unruptured aneurysm.—Softening by compression of part of the middle lobe [*sic*] of the brain

by growth of an aneurysm of the carotid canal and resulting hemiplegia was recorded by Bartholow (1872). He also reported contralateral hemiplegia from pressure on the crus cerebri by an aneurysmal mass. Aneurysm may therefore act the part of a tumor mass. Beadles (1907) visited various museums which had examples of unruptured aneurysm, some of which were associated with motor tract compression and hemiparesis. Collier (1931) believed that to produce such local symptoms of compression the mass must of necessity clot partially or undergo calcification in its wall. Dandy (1944) and Doyle (1950) recognized the occurrence of hemiplegia from the mass of an expanding aneurysm without rupture. The latter author found such motor loss to be persistent rather than transient. In the fourth case reported by Jefferson (1937) the crus cerebri was indented by the aneurysm and an example of mid-brain compression was reported by Hyland and Barnett (1954), each of which was associated with hemiplegia.

Hemiparesis Irrespective of Bleeding

Propagation of thrombosis with occlusion of the parent vessel of the aneurysm.—Thrombosis within intracranial aneurysms is known to be common if not the rule. Spontaneous cure of aneurysms in other locations has been reported, including instances in which the lesion thrombosed with maintenance of the continuity of the parent arterial tree (Shumacker and Wayson, 1950). Dott (1932–33) noted an example of aneurysm which simulated a pituitary tumour and which underwent thrombosis, fibrosis and cure. Cessation of spontaneous bleeding from an intracranial aneurysm occurs because of clotting and thrombosis. That such a thrombotic process may not remain limited to the aneurysmal sac was a concept suggested by Biemond and ter Braak (1933) who stated that the thrombus could extend into the parent vessel and produce obstruction to blood with neurologic deficit. Sjöqvist (1936) reported a case of presumed thrombosis with blockage of the flow of the opaque material by angiography. Jefferson (1937) believed that thrombosis in normal cerebral arteries was so rare that when encountered the cause might be found in the presence of an aneurysm in the wall of the vessel. Dandy (1944) noted that hemiplegia was produced by direct extension of thrombus from the sac into the parent vessel. Courville and Olsen (1938) considered that such a sequence of events occurred, although rarely, following rupture. They emphasized that after rupture the clot extended into the parent vessel particularly when the aneurysm arose from the point of fusion of both anterior cerebral arteries or when both anterior cerebral arteries received the main flow from one internal carotid artery.

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Meadows (1951) also stated that focal neurologic symptoms could occur following hæmorrhage owing to obstruction of the artery issuing from the aneurysm by clot or by the aneurysm itself.

From this review and previous experience it is apparent that thrombosis may occur with or without rupture. When no rupture occurs the presence of an aneurysm as the cause may escape notice, a point made both by Jefferson (1937) and Robertson (1949). The case reported below clearly substantiates this thesis as does the report by Epstein (1953). The patient studied by the latter author showed signs of subarachnoid bleeding before death, but Epstein noted that the diagnosis of a major vessel thrombosis may be only a partial explanation if the co-existence of aneurysm is overlooked.

The thrombosis noted in association with aneurysm occurs, I believe, at, or distal to, the site of the sac. We have no evidence to support the proposition that aneurysm is associated with retrograde thrombosis into the carotid system or is ever responsible for cervical occlusion (*see* discussion by Johnson and Walker, 1951). That such a possibility exists, however, cannot be denied.

Case 3.—B. R. This 30-year-old man was admitted on March 9, 1953. Three years previously he had suffered the onset of intermittent episodes of right frontal headache, weakness and numbness of the left upper extremity. Such a episode began two weeks before admission and progressed until five days before entry. At this time, while stepping from an automobile, the patient collapsed to the ground with a left hemiplegia, loss of sensation over the left side of the body and some interference with vision.

On examination the patient's blood pressure was 150/80. He was stuporous but oriented. The right half of the calvarium was more prominent than the left, especially in the temporo-parietal area. An incomplete left homonymous visual field defect was present with normal visual acuity. The left side of the face was involved in a severe central type paralysis. Except for hip movements there was a left hemiplegia. The muscle-stretch reflexes were increased on the left. Sensory impairment on the left side of the body included touch, position sense and stereognostic sense. Thermal sensation was impaired in the lower extremity, and the pain and vibratory senses were distorted in their perception on the left. The cerebrospinal fluid revealed a pressure of 180 mm. of fluid and a total protein of 107 mg. per cent. Electroencephalography was abnormal with high amplitude, slow 1–3/second waves in the right fronto-temporal area. Plain skull roentgenograms disclosed a fine, 1·5 cm., curvilinear shadow of increased density, concave forward, arising upward from the centre of the sella turcica. Angiography on March 26, 1953, demonstrated complete blockage of the right intracranial portion of the internal carotid artery distal to the origin of the anterior choroidal artery (fig. 4). Ventriculography on April 20, 1953, showed dilatation of both anterior horns of the lateral ventricles. The inferolateral portion of the right anterior horn was indented and in juxtaposition to a 4 × 6 cm. area of multiloculated pockets of air in the right anterior temporal region (fig. 5). Surgical exploration disclosed the cortex to be softened along the inferior frontal convolution. An aneurysmal mass, measuring 2·5 × 2·5 cm. located within the Sylvian fissure, was completely filled with thrombus. The probable site of origin coincided with the

bifurcation of the internal carotid artery. Subsequent to craniotomy the patient made painfully slow improvement in strength in his paretic extremities.

The aneurysmal formation in this case did not fill angiographically and had it not been for the tell-tale calcification in the plain roentgenograms the true cause for the internal carotid artery occlusion probably would have escaped discovery.

Carotid system insufficiency.—Robertson (1949) reported 5 examples of ischæmic infarcts in his series of post-mortem examination of intracranial aneurysms. He suggested that these ischæmic changes might be due to a temporary spasm of the supplying vessels and further stated that some changes might be due to the compression of the arteries by the aneurysm but that more likely the latter had stimulated spasm even in vessels remote from the aneurysm. ter Braak (1950) also suggested that softenings might arise which were independent of hæmorrhage or thrombosis, and Meadows (1951) recognized ischæmia in the distribution of the middle cerebral artery as cause of hemiparesis in these cases.

That hemiparesis or focal deficit develops coincidentally with the occurrence of cerebral œdema in cases of aneurysms which bleed, thereby representing a cause and effect relationship, has been suggested by Courville and Olsen (1938), Dandy (1944), Doyle (1950) and Levin (1952). The mechanism of the œdema production, of course, remains unanswered, and this may be related in some way to a temporary circulatory insufficiency which permits irreversible tissue death.

Case 4.—S. T. D. A 56-year-old man was admitted November 1, 1952, in a semicomatose state. Two years previously he had suffered the onset of headaches. Since on the morning of admission he developed sudden occipito-vertical headache and lost consciousness, few other items in his history could be obtained.

At examination the patient's blood pressure was 150/100. He was comatose but moved his extremities in a defensive manner on painful stimulation of the right side. No left-sided movement was perceived. The pupils were large and equal, and reacted to light. Numerous flame-shaped and round hæmorrhages were present in the fundi, together with early papillœdema. Moderate nuchal rigidity was present. Tone was increased in the left upper and right lower extremities and plantar responses were extensor. The heart was enlarged. Lumbar puncture disclosed grossly bloody fluid with a pressure of 360 mm.

When the patient was seen in consultation four days later his right pupil measured 6 mm. and the left one 4 mm.; both reacted. The right lobe was abducted and evidenced a partial third nerve palsy. The left hemiplegia persisted. Right carotid angiography revealed a saccular aneurysm arising from the internal carotid artery at the site of the junction with the posterior communicating artery (fig. 6). This study followed by ligation of the right common carotid artery. Immediately following ligation the right pupil became smaller than the left (a stellate ganglion block on the right was done at the time of angiography, but no observation between block and ligation was recorded) The patient expired forty hours after ligation.

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Autopsy disclosed the right common and internal carotid arteries to be filled with ante-mortem clot from the site of ligation to the aneurysm, the latter being located at the bifurcation of the internal carotid artery. There was acute softening of the right cerebral hemisphere.

Ligation probably hastened this patient's demise by decreasing the blood flow to an already compromised vascular bed. How much of the ischæmic changes which were seen at post-mortem examination preceded the ligation is not known. Functionally the right hemisphere was deficient at the time of angiography. This deficiency was not due to major arterial occlusion, for the vascular tree was well demonstrated angiographically; and there was no evidence of intracerebral bleeding. I believe the ischæmic changes antedated the ligation, but were aggravated thereby.

The next case is a second example of this group in which hemiplegia occurs probably on the basis of some functional insufficiency with ischæmia.

Case 5.—S. G. M. A 43-year-old man was admitted to hospital on October 11, 1954, with a three-day history of sudden occipital headache, nausea, vomiting and bloody cerebrospinal fluid. At the time of initial examination his blood pressure was 112/60. He was awake but irritable and restless, showing signs of meningeal irritation. During the night eight days from the onset of his illness he became disoriented and aphasic with hemiplegia on his right side. Electro-encephalographic study disclosed a slow-wave focus in the left frontal temporal area. During the hospital course prior to surgical consultation his mental state improved but the hemiplegia and aphasia persisted. The extremities were equally paralysed and the face was included in the paralysis. No visual defect was demonstrated, although the right pupil was slightly larger than the left. The right abdominal reflexes were decreased, while the plantar responses were bilaterally flexor. Angiography performed on December 1, 1954, seven weeks after the onset of the illness, demonstrated an aneurysm arising from the left anterior cerebral artery distal to its junction with the middle cerebral artery (fig. 7). There was no angiographic evidence of intracerebral bleeding, nor was any major arterial thrombosis demonstrated.

Craniotomy disclosed a relaxed brain, and no evidence of intracerebral clot was present. A clip was placed across the neck of the aneurysm. The neck fractured at the junction of the aneurysm with the parent vessel. The internal carotid artery was then clipped but the lesion continued to bleed briskly. Next the anterior cerebral artery was clipped distal to the lesion. The bleeding was appreciably decreased but only after the middle cerebral artery was occluded did the bleeding cease. Post-operatively there was no increase in the patient's neurologic deficit. Angiographic studies after operation showed filling of the occluded middle cerebral artery territory via supra-Willisian channels.

The ætiology of the hemiplegia in this case is in all probability related to the presence of the aneurysm. That some form of functional impairment of circulation caused tissue death without leaving clues of the way in which this was caused seems clear.

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A third demonstration of the relationship between vascular insufficiency and aneurysm is exemplified by the next case with reasonable certainty although confirmation of the ætiology of the findings is still wanting.

Case 6.—E. L. Y. A 26-year-old truck driver was admitted on July 10, 1952. One year previously he had noted the onset of intermittent frontal headaches associated with blurred vision. Three days before admission, during sexual intercourse, he vomitted and lost consciousness. He awoke with a severe fronto-vertex headache and neck stiffness.

On examination the patient's blood pressure was 120/80. The man was awake and oriented but he complained of a severe head pain and his neck was stiff. The right optic nerve head was blurred, while both pupils were small and responded sluggishly to light. The left muscle-stretch reflexes were increased. Lumbar puncture revealed blood-stained cerebrospinal fluid at a pressure of 580 mm. of water. The cerebrospinal fluid and blood serology was negative.

Two days after admission the patient became more lethargic, and on the third day he suddenly developed a left hemiplegia and sensory loss. When seen in consultation, the patient demonstrated an incomplete left homonymous hemianopia and a flaccid left-sided paralysis, which was associated with increased muscle-stretch reflexes. A ptosis of the left eyelid was noted. Hypalgesia was present over the left half of the face, trunk, and extremities. He talked, but there was a left-sided masseter and pharyngeal muscle weakness, and the tongue deviated to the left.

Five days after admission bilateral carotid angiography demonstrated a filling defect of the extracavernous portion of the right internal carotid artery just before its termination, suggestive of a "negative" shadow which caused a bifurcation of the opaque material in the course of the vessel (fig. 8). In the anterior-posterior projection this area appeared as an attenuation of the vessel diameter. The patient showed no improvement and his right pupil became dilated. Two days following angiography examination of the cerebrospinal fluid showed that the pressure had fallen to 280 mm. of water and it was xanthochromic. Speech became less fluent and the patient became childlike and incontinent. Angiography was repeated on September 2, 1952. No aneurysmal sac was seen but multiple nodulations were present along the course of the right internal carotid artery within the cavernous sinus and distal thereto. Ventriculography on September 11, 1952, revealed a moderate degree of hydrocephalus and a shift of the septum pellucidum toward the side of a dilated right lateral ventricle (fig. 9). The patient showed evidence of severe focal and diffuse brain disease and subsequently required institutional care.

An extensive vascular occlusive component in the process has not been conclusively demonstrated in this case but in the absence of demonstrable intracranial masses the suggested explanation for the findings is a circulatory insufficiency of a degree and duration to leave permanent loss of substance in the hemisphere. The evidence that this insufficiency was due in large part to disease (aneurysmal dilatations ?) along the right internal carotid artery is, however, circumstantial.

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Summary and Conclusions

Six cases studies are presented to illustrate probable mechanisms in the production of hemiparesis by intracranial aneurysms of the congenital, developmental type. The various possible mechanisms suggested and established in the literature are reviewed. Certain of these, such as the occurrence of intracerebral hæmorrhage, are well-founded and need little emphasis. I would suggest that other mechanisms such as functional circulatory insufficiency may lead to tissue death in the absence of major vessel occlusion and deserve careful study. It may also be worth emphasis that major intracranial vessel occlusions in young adults may be found associated with an aneurysm as the underlying cause.

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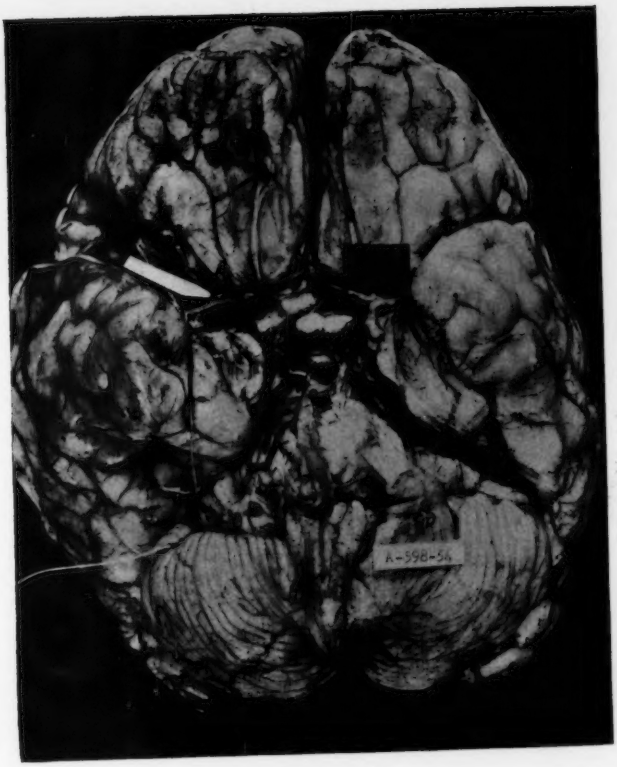

FIG. 1.

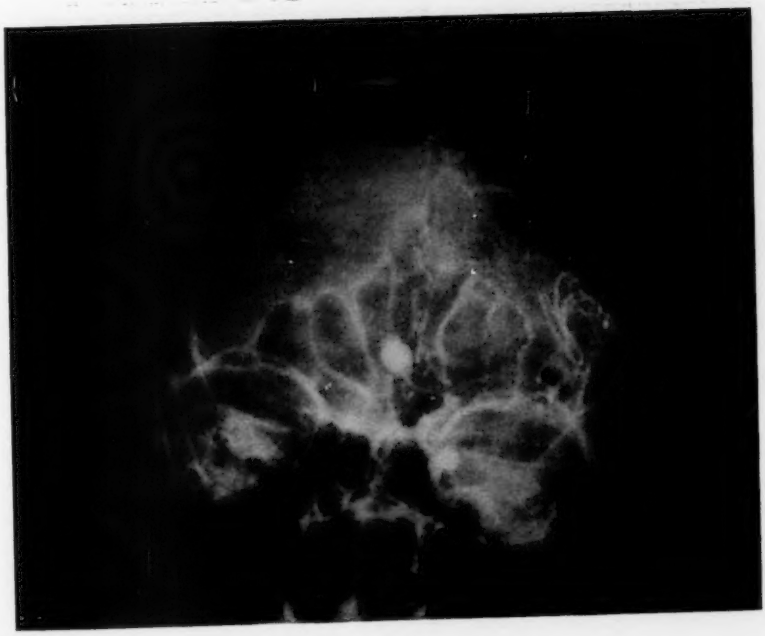

FIG. 2.

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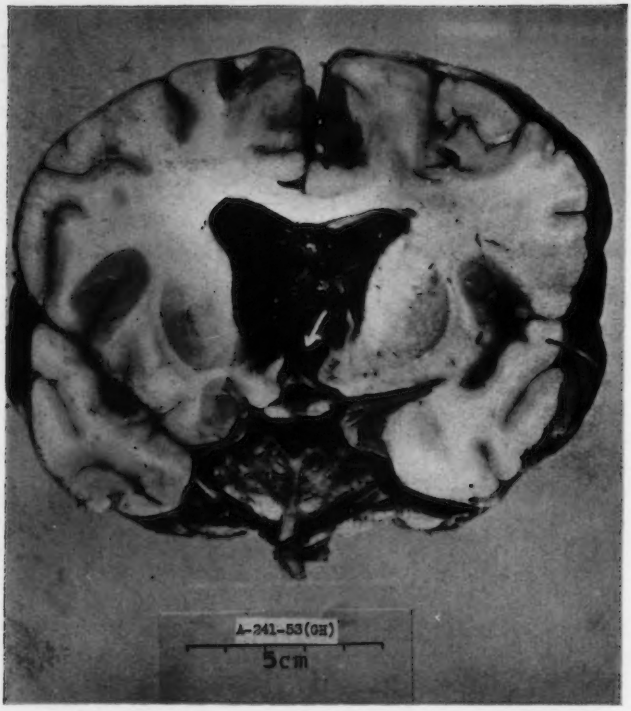

FIG. 3.

FIG. 4.

To illustrate article by W. Eugene Stern.

PLATE XLIV

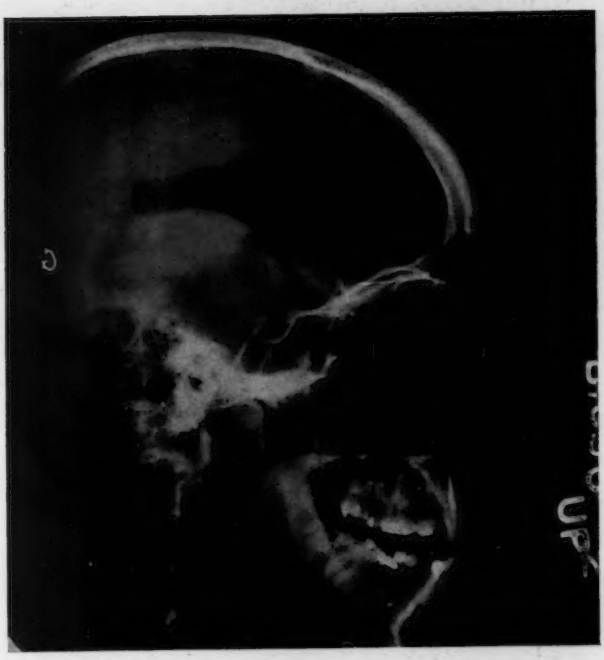

FIG. 5.

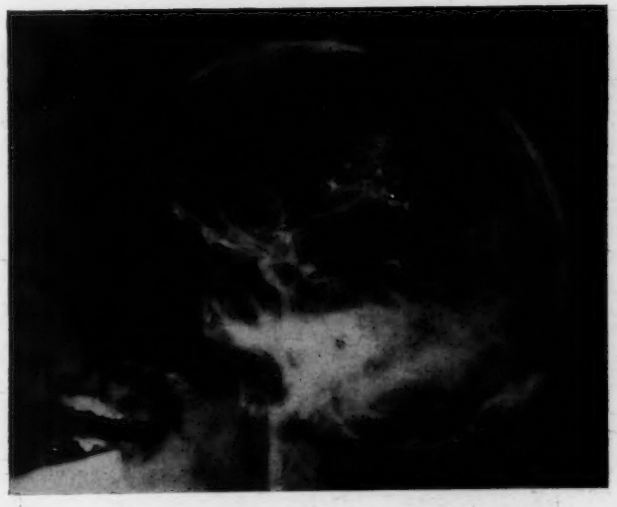

FIG. 6.

To illustrate article by W. Eugene Stern.

XUM

FIG. 7.

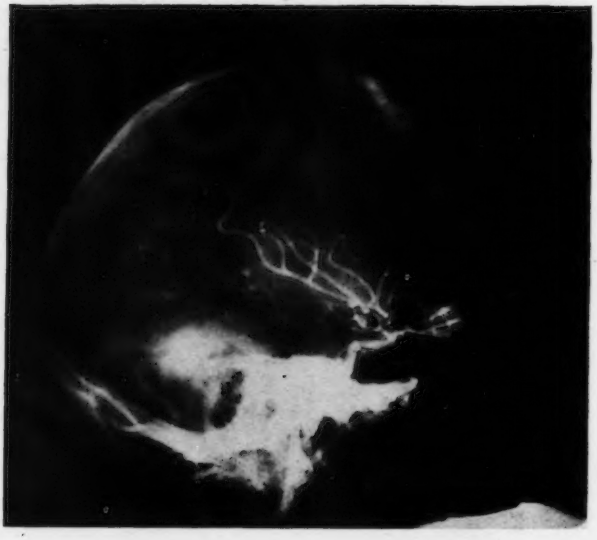

FIG. 8.

To illustrate article by W. Eugene Stern.

PLATE XLVI

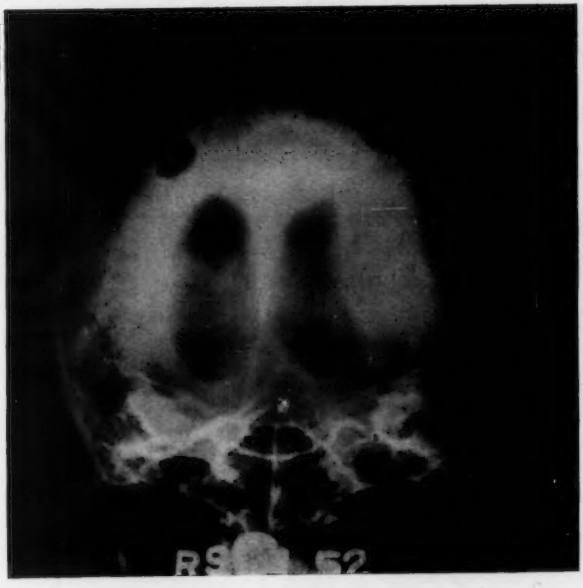

FIG. 9.

To illustrate article by W. Eugene Stern.

LEGENDS TO PLATES

PLATE XLII

FIG. 1 (*Case* 1).—Autopsy specimen showing swollen right cerebral hemisphere and the sites of the two aneurysms. The massive intracerebral hæmorrhage occurred from the right-sided lesion.

FIG. 2 (*Case* 2).—Left carotid angiogram demonstrating anterior cerebral artery aneurysm. The fundus of which tips toward the right side of the mid-line.

PLATE XLIII

FIG. 3 (*Case* 2).—Autopsy specimen showing aneurysmal sac (arrow) with rupture into lateral ventricular system maximal on the right (cf. fig. 2).

FIG. 4 (*Case* 3).—Right carotid angiogram demonstrating blockage of the vessel near the origin of the anterior choroidal artery.

PLATE XLIV

FIG. 5 (*Case* 3).—Ventriculogram demonstrating multiloculated pockets of gas near the Sylvian point on the right side (cf. fig. 4).

FIG. 6 (*Case* 4).—Right carotid angiogram demonstrating aneurysm at junction of internal carotid artery and posterior communicating artery.

PLATE XLV

FIG. 7 (*Case* 5).—Left carotid angiogram demonstrating the globular aneurysm at the origin of the anterior cerebral artery.

FIG. 8 (*Case* 6).—Right carotid angiogram demonstrating apparent filling defect at termination of internal carotid artery.

PLATE XLVI

FIG. 9 (*Case* 6).—Ventriculogram demonstrating enlargement of the lateral ventricles with the greater dilatation on the right side being associated with slight displacement towards the right.

XUM

RHESUS INCOMPATIBILITY AND MENTAL DEFICIENCY

BY

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RHESUS incompatibility as a cause of mental deficiency is now well recognized (Penrose, 1954). Fortunately, only about one child in 20, potentially incompatible with its mother, has hæmolytic disease (Race, 1954) and of these, especially since the introduction of effective treatment, only a small number suffer severe brain damage.

Already in 1875 Orth was interested in brain damage resulting from icterus gravis neonatorum, long before Landsteiner and Wiener discovered the rhesus factor in 1940. Schmorl reported nuclear damage in the brain of jaundiced babies in 1904. Until recently little attention was paid to the neurological effects in survivors of icterus gravis neonatorum and the causal relationship was not appreciated. Following the publications by Zimmerman and Yannet (1933 and 1935) the relationship between jaundice of the newborn and mental defect, epilepsy and extra-pyramidal symptoms began to be mentioned in textbooks of neurology (Brain, 1947).

Once discovered, this relationship became overestimated, as so often happens in such cases. Yannet and Lieberman (1944), as well as Snyder, Schonfeld and Offerman (1945), suggested that undifferentiated mental defect, with no history of jaundice, might be due to blood incompatibility: but it now seems clear that gross brain damage and mental defect can only arise from such incompatibility following severe jaundice (Pickles, 1949). The work of Gerver and Day (1950) suggests, however, that some loss of intelligence without gross neurological signs may follow icterus gravis.

A small proportion of children certified as mentally defective owe their handicap to blood group, usually rhesus, incompatibility. Most clinical articles on blood group incompatibility deal with the acute illness and there have been few accounts of the neurological after-effects.

Richards (1950) described 5 cases of double athetosis, deaf mutism

and mental deficiency, including one from the Fountain Hospital which is included in the present series. In 2 other of Richards' cases there was a history of neonatal jaundice. In the fourth case the child was rhesus positive but no parents or history were available. Only in the fifth case could blood group incompatibility be excluded. Other earlier accounts give clear descriptions of the neurological complications though they do not mention the rhesus factor. Schachter (1947) described an extrapyramidal syndrome in a second child following familial icterus ("Pfannenstiel's disease"). Intense jaundice developed and on the tenth day she had convulsions followed by weakness of the left side. She only learned to walk at 4 and she was placed in an institution for backward children. She learned to speak but had dysarthria and *bilateral auditory hypoacuity*. She was athetotic and the facial muscles were continually contorted into grimaces involving lips, cheeks and jaws. The athetosis was much worse during voluntary acts. The Babinski signs were negative. The patient was considered feeble-minded (*peu douée*).

Coquet (1944) in describing 5 cases of double athetosis following icterus gravis, gives good illustrations of expression and stance; he also clearly describes the evolution of the neurological picture through an initial period of rigidity and opisthotonus with convulsions, to a later stage of choreo-athetosis. His first case was a *deaf mute*. He does not mention the rhesus factor.

The clinical manifestations of residual brain damage after icterus gravis neonatorum are commonly regarded as due to lesions in the basal ganglia, viz. the globus pallidus and corpus Luysii. Some authors have mentioned, however, the occurrence of other, widespread lesions in the nervous system. Apart from cases dying in the acute phase of the disease there are 17 descriptions available of the morbid anatomy of patients with residual lesions; some of these of doubtful ætiology. In the acute cases there is a variable distribution of bile-stained foci. According to Becker and Vogel (1948) the basal ganglia, cerebellum and medulla are most often affected. There is a wide gradation of degenerative processes in the nerve cells throughout the nervous system including the cerebral cortex (Bertrand, 1946).

Those infants who survive the acute illness probably have similar but less marked changes in the brain. Those dying after the first few weeks no longer show bile staining but other changes in the brain have begun to make their appearance; these are outlined in the recorded cases (Table I).

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TABLE I

Case	*Author*	*Age*	*Chief clinical features*	*Structural changes*
1	Hoffman and Hausmann (1926)	3½ months	Icterus at 4 days. Twitching. Rotation of eyes. Spasm of limbs. Hypertonic. Opisthotonos	Persistence of yellowish tinge in basal ganglia. Other changes only microscopical. Perivascular round cell infiltration in basal ganglia and hippocampus. No definite nerve cell changes. Hæmosiderosis of the liver
2	Burghard and Schleussing (1933)	5 months	Neonatal jaundice. Yellow C.S.F. Convulsions. Opisthotonos at 5 days. Hypertonia. Early optic atrophy. Development of generalized œdema. Grimacing. Squint. Profuse sweating.	Yellowish-grey staining of grey matter in pallidum, corpus Luysii and Ammon's horn. Lesser staining in other parts. Some focal softening of white matter in both hemispheres. Destruction of nerve cells with proliferation of glial cells, especially in hippocampus
3	de Lange (1934)	6 months	Neonatal jaundice. *Petit mal*. Hypertonia. Opisthotonos. Failure of development	Only basal ganglia examined. Lack of vertical striation in globus pallidus. Loss of nerve cells in caudate nucleus, globus pallidum and putamen. Poor staining of myelin in globus pallidum and corpus Luysii
4	Zimmerman and Yannet (1935)	3 years	5 weeks premature. Icterus gravis. Rigidity Opisthotonos. Optic atrophy after 5 months. Athetosis. Mental retardation	Demyelination of optic nerves, white matter around posterior horns of lateral ventricles, peripheral part of spinal cord. Fascia dentata and end-plate of lamina parietalis of hippocampus destroyed. Loss of large nerve cells in corpus striatum, and globus pallidus. Absence of myelinated fibres in globus pallidus. Corpus Luysii almost completely disappeared. Paucity of nerve cells in red nuclei
5	de Lange (1935)	7½ months	One of twins both of which had neonatal jaundice without erythroblastosis. Hypertonia. Rickets. Retarded development	Yellow staining of flocculus, inferior olives, floor of IV ventricles, Ammon's horn, thalamus, putamen, globus pallidus and habenular nucleus. Degeneration of nerve cells in inferior olives, globus pallidus and putamen. Iron and bile pigment in liver. Cellular proliferation in portal tracts
6	de Lange (1936)	6 months	Neonatal jaundice. Slight enlargement of liver and spleen. Hypertonia. Head retraction. Rigidity	Absent striation in globus pallidus with loss of nerve cells. Poor staining of myelin in globus pallidus and corpus Luysii. Slight loss of cells in dentate nucleus. Some deficiency of myelin in frontal and temporal lobes. Corpus callosum and anterior commissure small. Certain cytoarchitectonic abnormalities of cerebral cortex
7	Biemond and van Creveld (1937)	3 months	Neonatal jaundice and umbilical sepsis. Rigidity. Opisthotonos	Absent striation of globus pallidus. Demyelination of globus pallidus and corpus Luysii. Loss of nerve cells and gliosis in demyelinated areas. Corpus callosum and fornices small
8	Biemond and van Creveld (1937)	4 months	Neonatal jaundice and umbilical sepsis. Slight anæmia. Extrapyramidal signs with rigidity and opisthotonos	Slight yellow staining of globus pallidus and corpus Luysii. Absent striation of globus pallidus. Marked demyelination of globus pallidus and corpus Luysii with loss of nerve cells. Corpus callosum and fornices small

			with rigidity and opisthotonos	Corpus callosum and fornices small
9	van Westrienen and de Lange (1937)	About 1 year	Icterus gravis, convulsions, opisthotonos. Profuse sweating. Clasp-knife rigidity	Blurred striation of globus pallidus with some shrinking of nerve cells and proliferation of glial cells. Greater proliferation of glia in striatum. Subthalamic nucleus small. Poor staining of myelin in globus pallidus
10	Zimmerman (1938)	11 months	Neonatal jaundice. Spasticity. Head retraction. Convulsions	Focal loss of nerve cells in caudate nucleus, putamen, dentate nucleus, inferior olives and cerebral cortex
11	Fitzgerald, Greenfield and Kounine (1939)	4½ months	Neonatal jaundice	Bilateral sclerosis of globus pallidus with an almost total disappearance of nerve cells. Considerable loss of nerve cells in corpus Luysii with dense fibrous gliosis. Ammon's horn and fascia dentata sclerosed
12	Fitzgerald, Greenfield and Kounine (1939)	1 year	Neonatal jaundice	Basal ganglia, particularly the globus pallidus shrunken and white. Moderate cell loss in globus pallidus with poor staining of myelin. Corpus Luysii sclerosed. Appearance of cortical nerve cells suggestive of lack of differentiation
13	Sobel and Zucker (1940)	4½ years	Neonatal jaundice, erythroblastosis and anæmia. Opisthotonos. Spasticity and choreo-athetosis	Moderate dilatation of ventricles. Poor staining of myelin in globus pallidus and corpus Luysii. Loss of myelin in pyramids. Decrease in number of nerve cells in layers 3 and 4 of cerebral cortex with proliferation of glia in cerebrum and diencephalon
14	van Bogaert (1947)	2½ years	Neonatal jaundice. Opisthotonos. "Decerebrate" position of upper limbs. Development of choreo-athetosis	Atrophy of corpus Luysii and, to a lesser degree, of globus pallidus. Slight degenerative changes in cerebral cortex
15	McLardy (1948)	2 years	Mother rhesus negative. Severe neonatal jaundice. Very retarded development	Bilateral shrinking of globus pallidus with almost total demyelination and fibrous gliosis. Putamen and caudate nucleus show conspicuous demyelination of large radial bundles. Complete degeneration of corpus Luysii and degeneration of nerve cells in pyramidal layer and fascia dentata of hippocampus
16	Mann and Courville (1948)	7 months	Neonatal jaundice	Paucity of nerve cells in dentate nucleus, putamen and globus pallidus. Occasional perivascular sclerosis with increase of glia. Many cells in substantia nigra vacuolated with indistinct outlines
17	Christensen and Vestergaard (1949)	22 years	Mental defective	Internal hydrocephalus. Moderate atrophy of basal ganglia. Peculiar microscopical yellowish pigment. Some degeneration of nerve cells in cerebral cortex and Ammon's horn. Softening in white matter

The object of this paper is:

(1) to discuss the existence among mental defectives of a group due to rhesus incompatibility

(2) to consider the typical and atypical clinical and morbid anatomical features, and

(3) to mention some of the special problems of a psychological and educational nature.

The survey is qualitative rather than quantitative since, particularly in the older patients, adequate histories are not always available.

(The frequency of this condition as a cause of mental deficiency has been surveyed by McKenzie, 1947, and by Scholl, Wheeler and Snyder, 1947, and as a cause of cerebral palsy by Asher and Schonell 1950.)

The cases reported are drawn from the population of the Fountain Hospital which provides for some 800 patients, mainly children of idiot or imbecile level under the Mental Deficiency Acts.

Case Reports

(1) P. B. Born 26.5.36. Admitted 6.1.39.

Family history.—The patient was the first child but the mother had had two transfusions prior to the pregnancy, one of which in 1929 was said to have been "wrong." The mother is group A, rhesus negative, the father group A, rhesus positive, presumably heterozygous. The mother's blood in April 1950 contained an atypical antibody and on August 6 an antibody acting in albumin was found, titre anti-D 1/512, anti-C 1/16. Both parents are of normal intelligence. The father is a railway porter, the mother was an upholsterer.

The second child, aged 13, is rhesus positive. She was deeply jaundiced within twenty-four hours of birth, but the mother refused transfusion. This child attended school but was said not to be intelligent and to have a "lazy brain," having "managed to keep out of an educationally subnormal school" but remained a source of concern to her parents. The third child was rhesus negative, but is said also to have been jaundiced after birth, though apparently not severely, and is of normal intelligence, being bright by comparison with her sister, at the age of 10. The fourth and last child, a boy, was stillborn. He was estimated to have been dead some ten days at birth in August 1949. There is no family history of mental or brain disease, except that an aunt, who is said to have had encephalitis, died in a mental hospital, aged 23.

Personal history.—He was born after prolonged labour in St. Bartholomew's Hospital where he and his mother remained for three months. Birth weight was 7 lb. Jaundice appeared rapidly and, by the fourth day, was intense. He was given injections of 5 c.c. of paternal blood intramuscularly on the fourth and eighth days, and on the ninth he had a blood transfusion, presumably also paternal, of 100 c.c. At intervals of a week he had 50 and 90 c.c. of maternal blood intravenously, followed ten days later by 100 c.c. of the grandmother's blood. This was thought to be the most effective transfusion and the baby went home a week later. At 7 months he could not sit and at 9 months did little with his hands. At 1 year he still did not sit unsupported and was diagnosed as a case of "kernicterus" at 21 months. He then showed a combination of rigidity and athetosis.

On admission at 2 years and 8 months he was doubly incontinent, had no speech, was spoon-fed and he could not walk. He grasped objects but soon dropped them. Purposeless movements and unintelligible noises were noted. He was deaf. Though friendly he showed little apparent interest and was considered to be a low-grade imbecile.

Progress was interrupted by respiratory infection. At 5 years he was athetotic but not spastic and there was a pseudo-Babinski sign. He stood, fed himself and played with toys but was still incontinent. At 7 he walked, obeyed gestures and laughed explosively.

Further progress.—At 16 he was under average height and weight (7 st.). He had a bilateral mastoidectomy scar. Apart from athetosis no clinical abnormalities were noted in the nervous system. Between spasms muscle tone was low and the plantar responses flexor. The athetosis ceased during sleep. He was deaf for speech but responded to loud noises sounded behind his back without warning. Although able to get about the hospital grounds on his own his athetosis was very severe, involving the entire musculature and every voluntary action cost him great effort. In walking there was constant swaying of the trunk, with extensive compensatory movements of the upper limbs. His neck twisted, snake-like, when he looked to the side. The facial movements were most characteristic and ceased only in sleep. The facial and jaw muscles and the tongue were continually involved in writhing and grinning movements. At times the cheeks were blown out, at others it appeared as though he was struggling with a large sweet in his mouth. When walking the feet were thrown well forward, often with external rotation, the knees were held stiffly.

His speech was much distorted but he could pronounce some recognisable words of one syllable which he had learnt with the assistance of the speech therapist and a deaf-aid. He understood some speech with the apparatus and the main handicap to voice production appeared to be dysarthria.

Despite his handicaps he succeeded remarkably well in much of what he undertook. This was largely due to his enterprise, endless patience and constant good nature. He won the sack race in the hospital sports against boys without any specific physical handicap, despite the fact that the least effort made him dyspnœic owing to his uneconomical use of muscular energy, and, that excitement increased the athetosis. He fed himself without spilling anything and was able to dress. By dint of tremendous concentration he could even write. He copied simple pictures on the blackboard with remarkable accuracy in spite of much athetotic movement of the hand muscles and difficulty in steadying the shoulder. He did simple basket making, weaving and knitting. He was friendly, well liked and took an active interest in whatever was going forward in the hospital.

At the age of 12 an attempt was made to administer standardized psychological tests. He scored an intelligence quotient of 31 on the Merrill-Palmer scale but this was considered to have little significance as he was penalized by deafness on the verbal items and by his athetosis in manual tasks. When he was aged 13 he was given the Drever-Collins Scale and Raven's Matrices (1938); he scored an I.Q. of 57 on the former and an I.Q. of 64 on the latter. He behaved with his usual good humour and showed initiative and independence.

A course of lysivane produced no improvement in his athetosis.

The usual laboratory tests revealed no significant abnormalities. The EEG showed a clear dominant rhythm at about 10 cycles per second blocking with eye opening. Muscle artefact obscured the record which was probably normal. Blood groups were; O, cDe/cde, MN, S+, P+, Le−, K−, Lu−.

(2) C. M. H. Born 28.6.37. Admitted 13.6.40.

Family history.—The patient was the sixth child. The first-born aged 24 was

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normal, the second died of jaundice at 2 days, the third pregnancy miscarried and the fourth child was jaundiced but survived and is now 18. At the birth of the patient the father was aged 33 and the mother 41. There is no history of mental abnormality in the family. The father had blood groups, CDe/cde, B, M, S, P−, Lu(a−), the mother; cde/cde, B. NsNs, P+, Lu(a−). In 1953 the mother's blood showed anti-D in the incomplete form.

Personal history.—The pregnancy was uneventful except for scarlet fever in the third month and labour was quick but normal. Birth weight 8 lb. Severe jaundice with some head retraction developed three hours after birth. She received 150 c.c. of maternal blood on the first day after which jaundice increased and anæmia and œdema appeared. A week later she was given 50 c.c. of paternal blood, after which the hæmoglobin level was 50 per cent. She was weaned at 4 months. At 7 months she showed little interest and did not sit up. She groped as though her vision was poor and tipped her head backwards. At 8 months she could eat solids and drank from a cup. At 3 years, before admission, she was said to take an interest in clothes and to like pretty things, also to be jealous of other children. She was said to scribble with a pencil in her left hand.

On admission, at 3 years, she could not walk or talk. She could not sit unaided, was incontinent and she had marked choreiform movements. She could not feed herself with a spoon, did not copy movements and did not respond to her name. She tried to speak but only made explosive noises. She played with a doll and seemed content.

Futher progress.—At 13 she was partly but not completely deaf. She turned when a bell was rung behind her. She understood clear conversational speech at two feet and responded to simple instructions. She could not stand without support on account of severe choreo-athetosis. She had difficulty in grasping objects which she did in a typically athetoid manner. She often dropped things and spilled her food out of her spoon. She looked like a child of 9. When excited her movements grew worse, her mouth "worked," she made clucking noises, her arms writhed, her head rotated and she was able to pull herself into a standing position for a brief time. She was able to say a few words quite clearly.

When she was tested on the Merrill-Palmer scale, she was alert, enterprising and co-operative. She took a lively interest in the test material but some of the tasks such as throwing the ball were beyond her by reason of her motor disability: she also failed tests involving form perception and manipulation, e.g. assembling a nest of cubes. On this scale she scored an I.Q. of only 20, but it was clear that this figure reflected the extent of her motor and sensory handicaps rather than her intellectual capacity. The Drever-Collins test at age 14½ gave an I.Q. of 34+.

The EEG showed some delta, alpha and beta activity in all areas, during sleep high voltage beta dominated. The record was considered normal for the age. The usual laboratory tests gave normal results. The Mantoux reaction was positive. The blood groups were as follows: B, MSNs, P+, R_1r, Lu(a−), K−, Le(a−b+), Fy(a+), Jk(a+b+).

(3) K. W. J. S. Born 31.5.44. Admitted 16.8.49.

Family history.—Both parents are stencil cutters, the father being 28 and the mother 21 at the birth of the patient. There is no history of mental abnormality in the family. The patient is the second child, the first, a girl, attends school and was not jaundiced. The father's blood groups are A, Rr, the mother's A_2, rr, NS, P+, Lu(a−), K−, Le(a−b+), Fy(a+). Her serum contained incomplete anti-D in 1953.

Personal history.—Pregnancy was uneventful but labour was prolonged. The baby weighed 9½ lb. A few hours after birth he became jaundiced. On the fourth day he was admitted to hospital as a case of erythroblastosis fœtalis, with tempera-

ture 100·8, pulse 140 and respiration 36. He was deeply jaundiced and there was much "bile" in the urine, the stools were dark. Neither spleen nor liver was palpable. On the fifth day the hæmoglobin level was 114 per cent but by the seventeenth it had fallen to 48 when, in view of the continuing jaundice, 10 oz. of rhesus-negative blood were given by intravenous drip. On the twenty-ninth day, the hæmoglobin was 90 per cent.

Backwardness was noted at 6 months when he failed to sit, and had a squint. At the age of 4 years he could not wash, dress or feed himself. The parents were not certain whether he could hear.

On admission at 5 years he weighed 28 lb. and had a head circumference of 20 in. There was no speech. A false Babinski sign was present with marked athetosis and he was very restless, could not sit without support and lay wriggling and twisting. He could see and grasped offered toys but could not feed himself and was doubly incontinent. He liked attention, smiled when stroked and struggled to investigate the sound of a bell. He was assessed as an idiot.

Further progress.—At the age of 9 he had changed little. He remained crippled by athetosis and got into all kinds of uncomfortable positions, his arms and legs becoming entangled. He was hypotonic between the spasms, tending to slip through one's hands when lifted under the armpits. He had a marked bilateral squint and was partly deaf. He was still doubly incontinent. He reached for everything offered to him with characteristic, undulating, convulsive movements. He could pull himself into a semi-sitting position by means of the cot rails. When grasping, his thumb was usually bent back stiffly, and the third and fourth fingers curled round the object, while the first and second jerked back, or the first and second fastened round it while the other two stuck out stiffly like the thumb.

He paid attention and watched alertly but made no response to spoken instructions and would not open his mouth or close his eyes on request. He seemed cheerful and appreciated attention. He could not speak but attracted attention by grunts. Athetoid spasm of the facial muscles was noticeable. On the Vineland Scale he had a developmental quotient of 8, which, again, is a reflection of his motor and sensory handicaps as much as of lack of capacity to comprehend.

The EEG showed low voltage activity, there were no alpha waves as the eyes remained open. There were traces of activity at 10 c/sec. The record was doubtfully normal. The usual laboratory tests gave no relevant results. The blood groups were as follows: O, MNS, P+, R_1r, Lu(a−), K−, Le(a+b−), Fy(a+), Jk(a+b−).

(4) S. W. Born 31.12.40. Admitted 22.12.48.

Family history.—The father, a club owner, and the mother, a cafe assistant, were intelligent and aged 31 and 33 respectively at the birth of the patient, who is the third child. The first sibling, a boy, won a scholarship. The second was slightly jaundiced for two weeks after birth but also won a scholarship. In 1943 the mother's serum contained rhesus antibodies. In 1952 anti-D was still present and her groups were: A_2, MS, P+, rr, Lu(a−), K−, Le(a−b+), Fy(a+). There was no record of mental abnormality in the family.

Personal history.—Birth was normal in spite of placenta prævia. Jaundice started on the first day and the child was ill for seven weeks. She progressed slowly and at 11 months had not sat up. At 4 years she tried to walk with support. Up to the age of 3 she had attacks of trembling which were diagnosed as *petit mal*. She had pneumonia three times.

On admission at 8 years she had generalized chorea. She weighed only 41 lb., her head circumference being 19¾ in. She did not respond to sounds but followed a light with her eyes. She had no speech but made sounds as though she were laughing. She was doubly incontinent, could not feed herself or stand, even with

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support. The left arm was contracted. She showed little interest in her surroundings and resisted attention. She would not imitate movements and flung toys away. She was difficult to feed and had several attacks of respiratory infection.

Further progress.—At 13 years there was chorea of limbs, face and eyes. When anything was placed in her right hand she would shake it and look at it but would not herself reach out for an offered object. She could feed herself with bread and butter but wasted most of it and she could not handle a spoon. She was doubly incontinent, had no articulate speech and her hearing was doubtful. The chorea became more marked with excitement. She made no attempt at walking or standing. She was very thin and lay in a padded chair tending to "tie herself into knots." The plantar responses were extensor with muscle tone normal between the involuntary movements, which were quick, jerky and non-repetitive with occasional slow, wobbling athetoid components.

She was not entirely unresponsive and smiled occasionally when spoken to. She did not try to copy movements and when given anything tended to put it into her mouth.

The EEG showed rather lower voltage than usual for her age. Some alpha activity at 10 c/sec. could be seen when muscle artefacts permitted. Slow activity was not excessive. The usual laboratory findings were negative. The blood groups were as follows : O, Lu(a−), K−, Rr, MNS, Le(a−b+), P+.

(5) J. L. F. Born 29.5.44. Admitted 12.11.46. This case was reported by Richards (1950).

Family history.—The father was a hospital porter, the mother a maker of surgical needles, their ages at the birth of the patient being 37 and 36 respectively. There is no family history of mental abnormality. The first child was stillborn, the patient is the second. The third child was a normal boy and the fourth pregnancy miscarried. In 1947 during the third pregnancy anti-D was present in the mother's serum in a rising titre. The mother was rhesus negative and the father positive (homozygous). Surgical induction at the 40th week produced a normal baby. No transfusion was given although the baby's hæmoglobin fell to 62 per cent on the 11th day. In 1949 saline and albumin antibodies were present in the mother and the Race Coombs test was positive.

Personal history.—Pregnancy and birth were normal but icterus gravis developed fourteen hours after birth and the baby was found to be rhesus positive. Three blood transfusions were given from other patients and a later one from the blood transfusion centre. His subsequent development was very slow.

On admission at the age of 2½ he weighed 30 lb. with a head circumference of 18¾ in. He stood with difficulty. He cried continually and could not speak. He did nothing for himself and appeared withdrawn, hiding beneath the bedclothes and rejecting toys. He was doubly incontinent. Six months later he walked unsteadily and stiffly but still could not feed himself. He was distractable and would not play constructively.

Further progress.—At 9 years he was active but clumsy. He was completely deaf and paid no attention to verbal instructions. He did not attempt to lip read and did not look at the face of the person addressing him. He walked on a broad base, being ataxic and falling readily. He was clean in his habits but could not yet dress. He used a spoon dexterously. He had left internal squint and nystagmus on fixing to the left. The ataxia was more noticeable in the legs but hand co-ordination was also poor. He moved rapidly at times with a festinating gait. There was no athetosis or chorea but the movements were inefficient and involved much unnecessary activity.

He was difficult to restrain but did obey visual instructions. He had the detached, unemotional expression of the deaf, but displayed a sense of humour. His

activity was purposeful and he managed to hold a pencil lightly in spite of his clumsiness. He rapidly learned to operate new things, e.g. a cigarette lighter and a toy car. He was attending the deaf class and making progress. He persevered doggedly with test items. He would tap the examiner's arm to gain her attention and point to what he wanted. His intelligence quotient on the Merrill-Palmer scale was 45 but this again reflects his sensory and motor difficulties. On the Drever-Collins scale he scored an I.Q. of 61+. He would wear a hearing aid but had developed little speech. He subsequently left hospital and is now attending a special school for the deaf.

The electroencephalogram was doubtfully normal for the age. The usual laboratory investigations were negative. The blood groups were as follows: O, Ms, NS, P+, CDe/cde, Lu(a−), K+, Le(a+b−), Fy(a+), Jk(a−).

(6) E. C. Born 16.9.41. Admitted 5.12.46.

Family history.—The father was a male nurse, the mother a domestic worker. They were 34 and 30 respectively at the birth of the patient. A paternal uncle attended a school for the educationally subnormal. The patient results from the second of four pregnancies. The first child, a girl, was "lazy at school-work." The third child born in 1947 became severely jaundiced on the first day. She received some 6 transfusions of rhesus-negative blood and in 1950 was doing well at school. The fourth pregnancy miscarried at 3 months. In 1950 the mother's serum contained anti-D and she was group O, Fy+, K−, rr.

Personal history.—Normal pregnancy and non-instrumental delivery resulted in a 7 lb. baby. Jaundice lasted five days (mother's recollection—records destroyed) with no blood transfusions given. At 2 months weakness of the left side was noted and at 14 months he was readmitted to hospital after a severe fit followed by coma. He began to walk at 2 years but was still unsteady at 5. He remained incontinent and had *petit mal*.

On admission at 5 years he had a spastic hemiparesis and walked unsteadily. He had little use in the left arm, said only a few indistinct words but was not deaf. He could not use a spoon or dress himself. The left plantar response was extensor with increased tendon-jerks.

Further progress.—At 12 he had improved slightly although the left side of the body was stunted. He used the left hand for auxiliary holding purposes. He showed little constructive ability. His speech was echolalic though clear. The left plantar response remained extensor and there was some slight athetosis on the left side. He had had one minor fit in two years. Athetosis only appeared during voluntary movement. The left pupil was larger than the right.

He was inquisitive, friendly, restless and garrulous. He persevered cheerfully at test items, using one hand for bead threading. He understood simple requests and showed initiative. He did not know colours. He liked attention. He achieved an intelligence quotient of 27 on the Terman-Merrill scale.

The electroencephalogram showed high voltage, slow spike and wave activity bilaterally symmetrical and "probably of thalamic origin."

He was tuberculin positive. The Wassermann reaction and parallel test were faintly positive on two occasions and subsequently negative, whilst the cerebro-spinal fluid was quite normal. Other laboratory findings were also normal. Air encephalography showed right sided cerebral atrophy, more marked in the posterior parietal region, with dilatation of the right ventricle.

The blood groups were as follows: O, R$_1$r, Ns, P+, Le+, K−, Lu−.

(7) S. E. C. Born 24.11.51. Admitted 2.2.53.

Family history.—The father was an engineer's mate. Both parents were healthy and aged 25 when the baby was born. The patient is the second child, the first one being normal. The mother was rhesus negative and had antibodies at the 37th

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week of the first pregnancy but the first child was so mildly affected that no treatment was given. The father was rhesus positive. There was no history of mental abnormality in the family.

Personal history.—The mother had a rising anti-body titre reaching 1/1,000 two months before delivery. Labour was induced at 36 weeks and a severely affected, 6 lb. infant was delivered. His cord hæmoglobin was 64 per cent and Coombs' test positive. After an exchange transfusion by the umbilical vein the blood bilirubin was 9 mg. per 100 ml. However, jaundice increased next day and a second exchange transfusion was given. On the 4th day "signs of kernicterus" appeared and jaundice lasted one month. At 2 months he was spastic but at 7 months had good head control. At 10 months he had crying fits.

On admission at 15 months he was accessible and cheerful, smiling when attention was paid to him, but he could not focus an object or support his head. He seemed to hear a bell. He had a grasp reflex but did not reach for objects. He could not chew, stand or walk. His teeth were stained yellow. The social quotient on the Vineland Scale was 33.

He died of pneumonia nineteen days after admission. Apart from the pulmonary changes the main abnormalities discovered at autopsy were in the brain, the weight of which was 1,050 grammes. There was congestion of the superficial veins. Coronal section showed reduction in size with absence of medullary pallidal lamination and slight discoloration of the globus pallidus anteriorly. The conspicuous changes were cellular sparseness in the superficial layers of the cortex and abnormality of the globus pallidus. The cellular sparseness was most marked in the frontal and occipital lobes, in layers II and III.

The myelin in the anterior part of the globus pallidus was abnormally pale in stained sections and there was a deficiency in the myelination of the large radial bundles of the putamen. The myelin sheaths were in various stages of breakdown. Similar appearances, but less pronounced, were present in other parts of the nervous system. There was much neutral fat in the globus pallidus and some fibrous gliosis but the number of nerve cells was only slightly reduced.

Some foci of dense fibrous gliosis spreading from the surface to laminæ I and II were present in the cerebral cortex; this was generalized in the hippocampus. Glial cells were slightly increased in number throughout the grey matter. Nerve cells stained unevenly with indistinct outlines and vacuolated cytoplasm. Nissl substance was absent in all but the largest. Many "ghost" forms could be seen. The thalamic and subthalamic nuclei were free of demonstrable change.

There was dense mural gliosis of the entire ventricular system and a layer of spongy degeneration midway between the outer pyramidal cells and the fascia dentata of the hippocampus. (A more detailed report of the morbid anatomical findings in this and the following case has been made elsewhere (Crome, 1955).)

(8) C. A. B. Born 3.11.50. Admitted 16.6.52.

Family history.—The father, a policeman, the mother, an assistant nurse, were healthy and were 26 and 31 respectively at the patient's birth. The patient resulted from the fourth of five pregnancies. The first two children attend normal school and were not jaundiced. The third child was severely jaundiced and lived only three days. He was born at home in 1945 and no transfusions were given. The fifth pregnancy was terminated at the fourth month. The father is rhesus positive and the mother negative with anti-D in her serum. Father O, MNSs, P−, R_2r, Lu(a+), K−, Le(a−b+), Fy(a+), Jk(a+). Mother O, MNSs, P+, rr, Lu(a−), K−, Le(a−b+), Fy(a−), Jk(a−).

Personal history.—Pregnancy was normal apart from severe whooping cough at 6 months. Labour was induced at 8 months and birth-weight was 3 lb. 7 oz. After breech delivery the infant was limp but cried well. Hæmoglobin was 88 per

cent and Coombs test positive. Despite replacement transfusion on the same day jaundice appeared on the third, and twitching, head retraction and rigidity on the sixth day. The cerebrospinal fluid was bile-stained on the seventh. On the 22nd day the hæmoglobin was 68 per cent and during the second month three transfusions of 30, 38, and 65 c.c. of packed cells were given. At 9 months she weighed 15 lb., was difficult, always stiff, could not sit up and showed choreo-athetosis. At 13 months she was restless, slept badly and refused to be left alone.

On admission at 19 months she could not walk, sit or do anything for herself. She would grasp an object placed in the left hand. She lay all day in opisthotonos and had spastic diplegia with athetosis of the face. She did not respond to speech. Her eyes followed bright objects and she tried to reach them. She opened her eyes when a bell was rung. She ceased crying if picked up. She had a developmental quotient of 15 on the Vineland Social Maturity scale.

The usual laboratory investigations were negative and the blood groups were: O, MNSs, P−, R_2r, Lu(a+), K−, Le(a−b+), Fy(a−), Jk(a+).

She developed pneumonia and died in status epilepticus a month after admission. At autopsy there was pulmonary œdema with lobular collapse. The brain was small, 819 grammes (normal 1,050 grammes). Coronal section showed faint bluish-brown staining of the globus pallidus which was poorly defined. Both globus pallidus and corpus Luysii were small. The main structural changes were similar to those in the previous case, cellular cortical sparseness being even greater. The myelin of the globus pallidus was only slightly paler than normal but showed breakdown on higher magnification, and fibrous gliosis was more marked than in the previous case. In this case also there were deficiencies in the large radial bundles of the putamen.

There was a uniform marginal fibrous gliosis over the whole of the cerebral cortex and brain-stem. The number of glial cells was slightly increased throughout the grey matter. Most of the nerve cells exhibited some degree of degeneration. The cortex and subcortical centres showed chromatolysis and many "ghost" forms. There was focal loss of the Purkinje cells with feeble staining of the remainder. There was also cell loss and degeneration in the dentate, inferior olivary and cranial nerve nuclei and in the anterior horns of the spinal cord. Mural fibrous gliosis was present throughout the ventricular system.

(9) P. N. Born 3.4.51. Admitted 14.7.53.

Family history.—The father, a telephonist, the mother, a milliner, both healthy, were 33 and 32 respectively when the patient was born. There was no family history of mental abnormality. The patient resulted from the sixth of seven pregnancies. The first child, now 10, is normal. The second was stillborn, the third miscarried, the fourth died at one week of jaundice, the fifth was a girl who was jaundiced at birth but is healthy. Her delivery was induced at 8 months and she had a blood transfusion immediately after birth. The last pregnancy was terminated and the mother sterilized. The father is CDe/CDe, and the mother, A, rr; at the 32nd week of her pregnancy with our patient rhesus antibodies were: albumin 1 in 8, saline nil.

Personal history.—The mother was sick throughout the pregnancy. Delivery was rapid and was surgically induced at the 8th month. Weight at birth was 7 lb. and at 36 days, 6 lb. 5 oz. The cord hæmoglobin was 60 per cent and direct Coombs' test strongly positive. The infant was pale and jaundiced with a very large liver and spleen. Despite an exchange transfusion signs of kernicterus developed on the 4th day. Serum bilirubin rose from 4·4 mg./100 ml. on the first to 33/100 ml. on the 5th day. She had heart failure and convulsions. At 2 years she could not walk or talk.

On admission at 2 years and 3 months she was a helpless idiot unable to sit,

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stand, walk or talk. She was doubly incontinent and could not feed herself. She had feeble blink and grasp reflexes, sucked her hand and was poorly developed with a small trunk. There was plagiocephaly, divergent squint and spasticity with a left extensor plantar response. The developmental quotient was 8. Usual additional laboratory findings were normal. She has made no progress, shows no signs of intelligence and has frequent attacks of respiratory infection.

(10) B.L. Born 19.11.36. Admitted 28.5.42.

Family history.—An illegitimate boy whose mother attempted abortion late in pregnancy. The father was in the Army, the mother's occupation was not known. She was 26 at the birth of the child and in good health. There is no known mental abnormality in the family.

Personal history.—He was born at the 7th month of pregnancy and weighed 3 lb. 5 oz. He was placed in an incubator and received oxygen for eleven weeks. The hospital records and the parents are not available but the aunts believe he was not jaundiced. At 2 years he could not walk or talk. On admission at 4 years he was spastic, could not walk and would not point to his features. He was restless, had unintelligible speech and nocturnal incontinence.

Further progress.—At 17 he seemed to hear fairly well. He had marked ataxia and athetosis. He was so like Case 1 that when the two were seen walking together it might be thought they were imitating each other. His speech was indistinct at times but it was quite easy to follow. He had some difficulty at times in distinguishing consonants and mistook "house" for "trousers," and so on. He protruded his tongue when concentrating, in fact his face, neck and trunk all "worked" with the effort.

He was co-operative and friendly, responding with alacrity to instructions. He recognized pictures, was clean, dressed himself and fed himself with a spoon. He showed initiative and patience. The Stanford-Binet I.Q. was 34, Raven's Matrices 36 and Drever-Collins 44. All of these underestimate his real ability.

The electroencephalogram showed only traces of alpha activity at the upper limit of normal frequency with diffuse, irregular, dominant theta activity. It was regarded as mildly abnormal. The usual laboratory findings were negative. The blood groups were: O, MsNs, P−, R_1R_1, Lu(a−), K−, Le(a−).

(11) R. R. Born 18.7.48. Admitted 2.2.50.

Family history.—The parents were brother and sister, being 34 and 40 respectively at the birth of the patient. The mother was a domestic worker and rather nervous. The father had been a prisoner of war and was psychopathic. The patient resulted from the sixth pregnancy. The first child, a boy by a different father was intelligent. The second, a boy, and the third, a girl, are by the legal husband and are normal. The next child, a boy, is, like the patient, the result of incest. He is said to have an I.Q. of 115. The 5th pregnancy, also incestuous, miscarried. The mother had a rhesus-positive transfusion a year before the birth of the patient and she was found to have rhesus antibodies before delivery. In 1950 she was cde/cde and had anti-D in the blood. The mother has since married again and has had a further normal child.

Personal history.—Labour was induced medically at 8 months. The birth weight was 7 lb. 5 oz. He was lusty at birth but within a few hours became deeply jaundiced, whilst the hæmoglobin fell to 70 per cent. The Race-Coombs test was positive. He was transfused immediately with 70 c.c. of rhesus negative blood. The hæmoglobin was 92 per cent when he left hospital, weighing 7 lb. 2 oz. At 6 weeks his colour was good and general condition satisfactory. The mother noted that he was retarded and considered him blind and deaf, and suspected epilepsy Later he was seen as an out-patient with a diagnosis of erythroblastosis fœtalis, hæmoglobin 66 per cent, red corpuscles 3·32 million/c.mm. and enlarged liver and

spleen. At 18 months he had ceased handling objects, could only sit unsteadily and was still bottle fed.

On admission at 19 months he was a blind and possibly deaf idiot. He took no notice of speech and did not speak. He could not stand, had no use in his hands, was doubly incontinent, was fed with difficulty and resented attention. He could sit, kneel, suck his fingers and whimper. He had nystagmus and some athetoid movements. The optic discs were normal but there was thinning of the retina with choroid showing through. He contracted enteritis, lost weight and died of bronchopneumonia and measles a year after admission. The electroencephalogram was almost completely flat. There was no significant rhythmic activity at any frequency even with the gains turned up and there was no alteration with eye opening and closure. The record resembled that in advanced Huntington's chorea. Routine laboratory tests were negative. The blood groups were O, R_2r.

At autopsy the body was emaciated, weighing 9·1 kg. There was bronchopneumonia. The liver and spleen were slightly enlarged, the former showing fatty change. Sudanophil-ether-soluble granules were present in the phagocytes in the lungs. After elimination of the lipoids from the liver with fat solvents it was possible to identify other sudanophil granules in the Kupffer cells. The latter were enlarged to 30 μ and had peripherally situated nuclei. The sudanophil granules were insoluble in a whole series of solvents. Similar cells were seen in the spleen and lymph glands.

The brain weighed 328 grammes (normal 1,100 grammes). The gyri were wasted and almost cartilaginous to touch. They were normal in number and position. The corpus callosum was thin and the ventricles dilated. The cortex was thin, the basal ganglia appeared normal except for pallor of the dorso-medial nucleus of the thalamus. The cerebellum was less affected.

Almost all the cells in the nervous system were affected by lipoidosis. They showed irregular ballooning of the cell bodies and dendrites, the nuclei being displaced. The adventitious substance was identical with that in the reticulo-endothelial system. Profound changes were also seen in the cerebral white matter. The myelin was pale and fibrous gliosis was widespread. There was little change beyond slight gliosis in the globus pallidus. The ganglion cell layer of the retina was depleted, containing few nerve cells, all of which showed neuronal lipoidosis.

Discussion

(*a*) *Frequency of the syndrome among mental defectives.*—The first 9 of the above cases are regarded as due to rhesus blood group incompatibility. In them, real or apparent mental defect dominated the clinical picture, with varying degrees of specific motor handicap or deafness in addition. These cases have been collected over a period of some six years so that they are drawn from a bigger number of mental defectives than the present population of the hospital. Over a similar period some 20 cases of phenylketonuria and 150 of mongolism were noted which makes it possible to form a relative impression of the importance of the rhesus factor as a cause of mental defect.

As mentioned it is possible that some cases have escaped recognition. For the past six years a specific question on neonatal jaundice has been included in the social history of all admissions. Information from other

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hospitals is available about the early history of most patients admitted. In selecting cases likely to be due to blood group incompatibility special attention was paid to patients with specific motor defect, deafness or a history of jaundice of the newborn. In the majority of instances these symptoms proved to be due to other causes. Blood was examined for antibodies from the mothers of some 40 cases of cerebral palsy, 28 with icterus neonatorum and 5 with deafness.

(*b*) *Nature of the syndrome.*—It is possible artificially to pick out a "typical syndrome" of rhesus factor brain damage, as illustrated by our first patient, P. B. This syndrome is not less distinctive than that of paralysis agitans. Like that disease, however, it may be produced by different agencies; rhesus incompatibility may also produce other neurological and mental symptoms. The "typical syndrome" consists of bilateral athetosis, deafness and mental retardation. There is also a "typical history" of severe neonatal jaundice, of a period of hypertonicity, often coming on during the jaundice and associated with convulsive attacks, followed later by reduction in tone and apparent improvement, only to be succeeded by involuntary and unco-ordinated movements. The movements in such cases are a spasmodic disorder of reflex tone and are "extrapyramidal" inasmuch as the plantar reflexes are flexor. Posture is particularly affected, as is the stability of the large muscles which is an essential basis for fine movements. The "typical" syndrome may well include some cases which have been described as "dystonia musculorum deformans," "athetose double" or Vogt's disease.

In fact, in only 1 of the 9 cases of rhesus incompatibility presented here is the "typical" syndrome present. The others exhibit wide variations in all of the three cardinal symptoms, intellectual, motor and hearing defect. "Kernicterus" is sometimes used as a term to describe these patients but, strictly speaking, its clinical use is open to question since actual kernicterus can only be demonstrated in neonatal fatal instances of the condition.

Since the clinical picture of brain damage due to blood group incompatibility is so unspecific, since also, other agencies may produce a similar picture, additional criteria for diagnosis must be sought. Diagnosis may be based on the following: (i) icterus gravis neonatorum; (ii) potentially incompatible blood groups as between mother and child; (iii) presence of specific antibodies in the mother's serum; (iv) a previous pregnancy or incompatible transfusion, and (v) clinical evidence of damage to the brain, e.g. intellectual, motor or hearing defect. However, even if all these criteria are satisfied other evidence may suggest that the

condition is not primarily or chiefly due to blood group incompatibility. For example, one of our patients, a mongolian imbecile, satisfied all of these requirements (although not athetotic or deaf) but we did not attribute his mongolism to this cause. The position is similar to that with regard to toxoplasmosis where there has been a tendency (Binkhorst, 1948) to attribute to this disease, any case of brain damage with a positive toxoplasmin test.

Cases 10 and 11 have been included in this series to illustrate the diagnostic problems. Case 10 suffers from a syndrome apparently due to icterus gravis neonatorum but probably not to rhesus incompatibility since he is Rh homozygous and both parents are therefore, presumably Rhesus positive. It is, however, possible that his mother was R′r (Cde/cde) instead of R_1r(CDe/cde), and could then have made anti-D. However this may be, he is after Case 1, the most "typical" of all those presented. (He is Kell negative so that Kell incompatibility can be excluded.)

Case 11 which will be reported elsewhere in detail (Crome, in press) also satisfies the criteria laid down, but the precise role of rhesus damage is doubtful. The lesions in the brain and elsewhere could be attributed to amaurotic idiocy and the fact that the parents are brother and sister can also be taken as contributory evidence for this diagnosis. On the other hand there was no family history of the condition, the family, for what it is worth, were not Jewish and the clinical course was unusual in that defect was present from birth. It seems possible that additional damage was done by the rhesus incompatibility and that the lipoidosis may have been precipitated in this way.

The case might also be quoted of E. C., not included in this report but published elsewhere. This child was mentally defective with a much impaired brain and a history of icterus neonatorum. He was rhesus positive and his mother negative with antibodies in her serum. This seemed a clear case of rhesus brain damage, but the jaundice was unusually mild and maternal antibodies were only demonstrated subsequent to the birth of this patient. Further, he had pitressin-resistant diabetes insipidus like other males in the sibship, which probably accounts for his mental defect.

The conclusion may be drawn that :

(1) there is a typical syndrome in survivors of severe jaundice of the newborn due to blood group incompatibility,

(2) that considerable variation with atypical cases occurs,

(3) that the "typical" syndrome may be produced by other agencies.

(*c*) *The motor disability.*—This varies very considerably in the

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different cases. As suggested there is a variation with age in the individual case. The symptoms also presumably vary according to the severity of the brain damage. Epilepsy seems to be rare after the initial hypertonic period.

The first 6 cases in this series show the more permanent aspects of the motor abnormality in its different forms. Athetosis varied from a form which still permitted active locomotion and constructive manual activity in Case 1, to complete crippling in Case 4 with Cases 2 and 3 occupying intermediate positions. It is, however, impossible to estimate the motor disability independently of general cerebral function and intelligence.

Case 5 shows a sharp deviation from the athetotic picture. His motor defect consisted essentially of clumsiness and lack of stability, of ataxia and did not at all resemble the other cases. The common feature with Case 1 was the remarkable manner in which he contrived to overcome his disability. Case 6 also seemed very different neurologically. He was not very different from many other cases of infantile hemiplegia, so much so that, taking into account the probable brief duration of the jaundice it seems possible that his condition is attributable to something other than rhesus damage.

Cases 7, 8, and 9 were too young to have arrived at the more lasting phase of the motor disorder, Cases 8 and 9 were in the transitional spastic stage, the former complicated by epilepsy. The motor disorder in Case 10 so closely resembles that in Case 1 that an identical lesion seems highly probable.

(*d*) *The deafness.*—This disability is also very variable. In Cases 1 and 5 the deafness was complete for all practical purposes. In Case 2 the deafness was only partial and there was sufficient hearing to allow of the acquisition of some speech by ordinary methods of teaching. Case 6 did not appear to be deaf, whilst Cases 3, 4, 7, 8 and 9 were at such a low mental level that adequate assessment of hearing was impossible. The attached audiograms obtained from the more co-operative cases show the extent of the hearing loss. Case 1 shows severe deafness throughout the hearing range, with the loss somewhat more marked for the higher tones. Case 5 shows an identical audiogram. Both of these boys were very co-operative and sufficiently intelligent for reliable results with the peep-show technique to be obtained.

(*e*) *The mental state.*—Some children who have suffered from icterus gravis are accepted as of normal mentality. Others, like the cases quoted here, are certified as mentally defective. In general the intellectual impairment and the motor defect go hand in hand and it is difficult to

separate one from the other. Standardized tests have very limited value for this purpose since they rely on actual performance, either verbal or manual and our patients were grossly handicapped in one or both of these respects. Of the different forms of cerebral palsy (Kirman; publication pending) the athetotic seems to be the least handicapped in respect of intelligence. Even formal testing showed Case 1 to be above imbecile level. The fact that Case 5 is educable has been recognized despite his relatively low test score. With these patients it is necessary to rely on general observation of behaviour, especially social behaviour, for an estimation of ability, rather than formal testing. Appreciation of situations, appropriate behaviour, efforts to assist other patients, solution of practical problems, awareness of relationships, are cues which point to relatively good preservation of general cortical function despite gross motor and sensory handicap. There is a real danger in some of these cases that educational opportunities may be missed if no attempt is made to disentangle the effects of the specific damage to particular functions from more general impairment of cerebral capacity.

As these cases illustrate, the degree of impairment varies very considerably. Cases 1 and 5 contrast with Case 4 who was an instance of profound idiocy. The others occupy intermediate positions.

Patients such as Case 1, may be suffering from a treble handicap, Indeed the effect of deafness and of athetosis may be so severe that it becomes something of an academic problem as to whether there is any reduction of intelligence in itself. The effect of the deafness in delaying development, particularly in regard to speech formation and social rapport is usually obvious, though it is possible that where the motor symptoms are conspicuous the sensory deprivation may be overlooked.

The effect of the motor difficulty on mental development may need a little more emphasis. Mental growth and maturation are based on experience. In a normal child a large part of this experience is gained by means of motor activity. Where motor performance is so badly organized as in the case of the severe athetotic this information is greatly reduced to the detriment of mental growth. In the normal child visual and auditory perception is continually linked with kinæsthetic impressions obtained in the course of handling, manipulating and using objects and in the course of active exploration of the environment. In very severe athetosis even the simplest aspects of these processes cannot be completed, e.g. the grasping of a toy to bring it into a favourable position for visual inspection and further manipulation. When the handicap is less severe the absence of locomotion may still narrow the mental horizon by limiting the part of the environment accessible to

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exploration. Apart from the quantitative poverty there is also a qualitative deficiency in kinæsthetic information in such children. Creative activity of gradually increasing complexity normally results in cerebral storage of an immense wealth of delicate kinæsthetic, adaptive patterns in the course of normal two-way interchange with the environment. The very nature of athetotic defect reduces this process to a clumsy and rudimentary exchange to the detriment of the mentality of the child.

Despite these handicaps and given good educational and social opportunities a large measure of compensatory adaptation can be achieved, involving the use of supplementary methods of dealing with the environment. The achievement of mobility, even if it be only in a wheel-chair, adds greatly to the breadth of experience. Similarly the child who is allowed to crawl actively on the floor has a better chance of development than the one who is confined to his cot. Successful adaptation is best seen in Case 5 of our series.

No marked personality deviations were noted in our patients who were distinguished by good humour and patience. Difficulties are most likely to arise in those of the rhesus-damaged children who are deaf. Case 5 showed some features of the detachment which develops in the deaf and up till recently was rather difficult to control when at home. Emotional difficulties with such children are not likely to be greater than with the deaf in general. They can be counteracted by inclusion in a deaf group, special instruction for the deaf, use of a hearing aid, the teaching of lip-reading, visual instruction, etc.

In general it is the more severely handicapped cases who are found in mental deficiency hospitals. Others who are more intelligent and less crippled are to be found in schools for the physically handicapped, in such units for the cerebral palsied as have been established and in schools for the deaf. Pentschew's (1948) material illustrates the relatively high level of development which may be achieved.

(*f*) *The pathology.*—The morbid anatomical findings in Cases 7 and 8 have been reported in more detail elsewhere (Crome, 1955). They are similar to those reported by the earlier workers mentioned above except that cortical lesions have received little attention previously. The characteristic features were widespread loss of nerve cells in the cerebral cortex and a more localized degenerative change in the globus pallidus.

The two main changes are not specific. Loss of cortical cells is a common finding in low-grade mental defectives. Damage to the globus pallidus is also quite common and is often due to anoxia. Cortical damage has not been mentioned in most of the previously recorded cases but this may be because its recognition is more difficult and because

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attention was focused on the basal ganglia. The deficiency of the large radial bundles has previously been noted only by McLardy (1948).

The variability of the neurological signs in the cases presented suggests considerable variation in the site and extent of the lesions in the nervous system. It seems reasonable to assume that the athetosis is associated with the lesions in the pallidum and subthalamus which are also mentioned by Pentschew and other workers. In connexion with the deafness the staining of the cranial nerve nuclei in the floor of the fourth ventricle noted in acute cases of kernicterus, may be relevant. It appears that there is selective vulnerability of these areas but as pointed out by Pickles (1949) further work on the late sequelæ is required.

Meanwhile it is possible to say that the clinical picture does not depend on the state of any one part of the brain but the function of the nervous system as a whole in relation to the environment. Thus, the emergence of athetosis after an interval of a year or so does not necessarily imply any gross extension of the cerebral lesions but is probably due to the development of function and maturation in that part of the brain which has escaped destruction. With the emergence of the capacity to attempt complicated actions requiring fine adjustment the deficiency in co-ordination is made obvious.

(*g*) *The electroencephalogram.*—The EEG in these cases is in no way distinctive. It has certain features in common with other forms of cerebral defect. The most striking finding is a relatively normal record, despite very gross interference with motor activity in Cases 1 and 10 and despite idiocy, presumably due to cortical destruction, in Case 4. The almost flat record in Case 11 certainly corresponds to the clinical and anatomical evidence that cerebral activity was almost absent. The findings in Case 6 are those to be expected in infantile hemiplegia with epilepsy.

(*h*) *The treatment.*—It is not possible to draw any statistical conclusions from this small number of cases. They do illustrate, however, the history of knowledge and treatment of this group of disorders. Cases 1, 2 and 10 derive from the period prior to the discovery of the rhesus factor. Treatment in the other early cases would be judged inadequate by modern standards (Mollison and Walker, 1952). It is interesting to contrast the early histories of patients 1–6, with Cases 7–9. Looking at these histories in the light of recent surveys (Walker and Nelligan, 1955), it seems probable that brain damage would have been prevented in the first group by the use of adequate exchange transfusion. The second group, however, were already affected at birth in contrast to the first group who were healthy when born. It is likely that but

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for the exchange transfusion they would have died. It is perhaps significant, in view of Walker and Nelligan's remarks on transfusion, that all the cases in the second group had an early induced labour.

The present position in regard to treatment of this particular cause of brain damage and mental defect is similar to that in other such treatable conditions, as for example, meningitis. A considerable number of children who would have been mentally defective but for treatment are now preserved from severe damage and grow up as normal children. On the other hand, a few, who remain a therapeutic challenge, survive as a result of treatment but are severely crippled.

(*i*) *Education.*—All of the children described in this report have been formally classed as ineducable. In Case 5 this decision has been reversed. The capacities of Cases 1 and 10 were probably not inferior to those of Case 5 and it seems possible that had more attention been given to Case 2 at an early age she also might have proved educable. Such patients do appear ineducable at first sight, doing badly on standardized tests which underestimate their real ability and understanding. In cases where there is any doubt as to the educability of the child there is no short cut to assessment which should be made primarily by the teacher with special experience of this type of handicap on the basis of at least six months' trial.

They need a great deal of special attention like other children with multiple defects. Attention must be paid both to the deafness and the motor handicap. To achieve success with the more severely handicapped cases the ratio between staff and pupils will need to be very high. In those affected by athetosis or ataxia the usual methods of instruction should be combined with a large amount of time devoted to opportunities to acquire manual and general muscular skill with emphasis on easy gradation of exercises, beginning with the crudest and simplest tasks which it may not be thought necessary to give to the normal child. Expert physiotherapeutic supervision is valuable but there does not seem to be any very special value in the different special therapeutic approaches for which specific claims have been made. Acquisition of appropriate responses to complex stimuli does take place in the athetotic child, though at a slower rate than in normal children. Since deafness is an even greater social handicap, if neglected, than is cerebral palsy, special training for the deaf should be given priority in those cases where there is a clash between the two forms of training. In general, treatment with muscle relaxants, and surgical interference have not proved useful in these patients.

The cases presented illustrate very well the fact that, with increasing

knowledge of ætiology, some cases of mental defect are preventable. Prior to 1940 the significance of the jaundice of the newborn might well have been passed over lightly and these patients included in the group of "primary amentia" or "neuropathic diathesis." It seems likely that further research will reveal other preventable causes of mental defect.

Summary

Nine cases of certified mental defect with a history of icterus neonatorum are presented. It is thought that the mental defect and brain damage are due to rhesus incompatibility. A tenth case with similar clinical features but probably not due to this cause and an eleventh where rhesus damage was complicated by lipoidosis are also reported.

The quality and extent of the damage varied very widely. A typical picture of athetosis, deafness and mental retardation could be recognized but may not be peculiar to this condition. Atypical pictures included ataxia and hemiplegia. The degree of mental impairment varied from complete idiocy to normal intelligence which was obscured by the multiple defect. Pathological studies showed widespread damage in the brain with emphasis on the globus pallidus but not sparing the cerebral cortex. The first 6 cases received no adequate treatment by modern standards and might have escaped brain damage if so treated. The last 3 affected at birth received modern treatment but for which they would probably have died. Three of the cases were potentially educable. Education of such cases needs much individual attention with special regard to deafness and ample opportunity for graded manual and general muscular training. The history of the study of rhesus factor incompatibility illustrates the preventability of certain forms of mental defect.

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DELAYED MYELOPATHY FOLLOWING ATLANTO-AXIAL DISLOCATION BY SEPARATED ODONTOID PROCESS

BY

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DURING recent years our understanding of neurological disorders associated with cervico-occipital bone pathology has been enhanced by several contributions.

Congenital anomalies are responsible for some cases. Two of the present authors (Barraquer-Ferré and Barraquer-Bordas, 1949) reported one instance of basilar impression with a deformity of atlas and odontoid subluxation. The patient made a good recovery after operation by Dr. E. Tolosa. In the same year one of us (Barraquer-Bordas, 1949) reviewed the cases of the same type in the records of the neurological and neurosurgical services in Barcelona.

After that Barraquer-Bordas, Bachs, and Modolell (in the Press) published another case of basilar invagination with an unusual symptomatology, a facial hemispasm which disappeared after surgical treatment.

In 1953 one of us (Barraquer *et al.*, 1953) published our first case of myelopathy due to atlanto-axial dislocation produced by a separate odontoid process.

The present paper concerns a second case of this pathology. We review also the cases that we have been able to find in the literature, and we discuss the anatomical, clinical and radiological aspects and surgical treatment.

Case Report.—J. C., a man 46 years old, was admitted in the Neurological Clinic of the Hospital de la Sta. Cruz y San Pablo of Barcelona on October 9, 1953.

History.—At 2 years of age he suffered a severe injury, when kicked in the frontal region by a horse. He was unconscious for an unknown length of time. Fourteen days later the wound was broken open when he fell out of bed, striking the left frontal region. Apart from this incident his recovery was uneventful and complete.

Except for a period of one month at age 14, when he had an illness character-

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ized by polyarthralgia, he remained well until he was 39 years old. At that time he noticed weakness of the legs when walking, more marked on the right. A year later weakness in the arms appeared. The tetraparesis increased until he was unable to walk unaided. He complained of pain in the back of the neck, aggravated by movements of the head and more pronounced in the morning, especially if he used a high pillow. Sphincter function was normal, although he complained of constipation for several years.

Neurological examination.—There was atrophy of the right sternocleidomastoid muscle. The patient had a spastic tetraparesis more accentuated on the right side, and more in the leg than in the arm. All deep muscle reflexes were hyperactive, those in the right being more brisk than those in the left. Babinski's sign was present bilaterally.

Except for a complete absence of vibration sense on the right side of the trunk and right extremities, sensory examination revealed no abnormality.

Crepitations were elicited on flexion and extension of the head. There was no spasm of the cervical muscles. The spine of the axis was abnormally prominent, while the depression immediately above it was unduly deep.

The patient was studied radiologically by one of us (A. M.).

Films taken with the neck in different degrees of flexion and extension (fig. 1) showed that the odontoid process was separated from the body of the axis. The dens had a constant relationship to the anterior arch of the atlas; but the mobility of the dens on the body of the axis was extreme. In the radiograph made with the neck in extension (fig. 1, A) the odontoid process bore a normal relationship to the body of the axis although a radiolucent line persisted between them. In the flexed position (fig. 1, B), however, the odontoid process and the atlas slid forward on the body of the axis, so that the distance between the spinous process of the axis and the posterior tubercle of the atlas increased from 9 mm. to 31 mm.

All films revealed rarefaction of the odontoid process and sclerosis of the adjacent margins of the odontoid and the body of the axis.

Lateral tomograms (fig. 2) demonstrated the dislocation of the odontoid process better.

Tomograms of the upper cervical spine were also made in the frontal plane (figs. 3, 4). In this way lateral flexion of the neck to the right and to the left revealed lateral inclination and shift of the dens on the body of the axis.

Thus the atlas and skull were able to slide freely on the superior surface of the body of the axis in all directions.

From the clinical and radiological findings it was concluded that the bony abnormality had resulted in severe compression of the anterior aspect of the spinal cord, by the posterior border of the superior surface of the body of the axis, especially when the head was in a flexed position, and also in lateral flexion.

It was felt that the abnormal positions and movements could be eliminated by atlanto-axial fusion and that this procedure would be more effective than any type of decompression.

We did not use the Guillaume technique (Guillaume and Lubin, 1941; Guillaume, 1952) because it would not have prevented the abnormal mobility in the lateral flexion of the neck.

The operation was carried out on October 24. The patient was placed in the prone position with the head moderately flexed. A vertical mid-line incision was made, down to the spinous process of the axis. The atlas was abnormally deep in the wound. Subperiosteal dissection of the cervical muscles was done with the point of a scalpel, while an assistant held the atlas with a forceps to prevent further anterior dislocation. The dura was separated from the bone with a small Deschamps dissector introduced extradurally and two wires were passed around

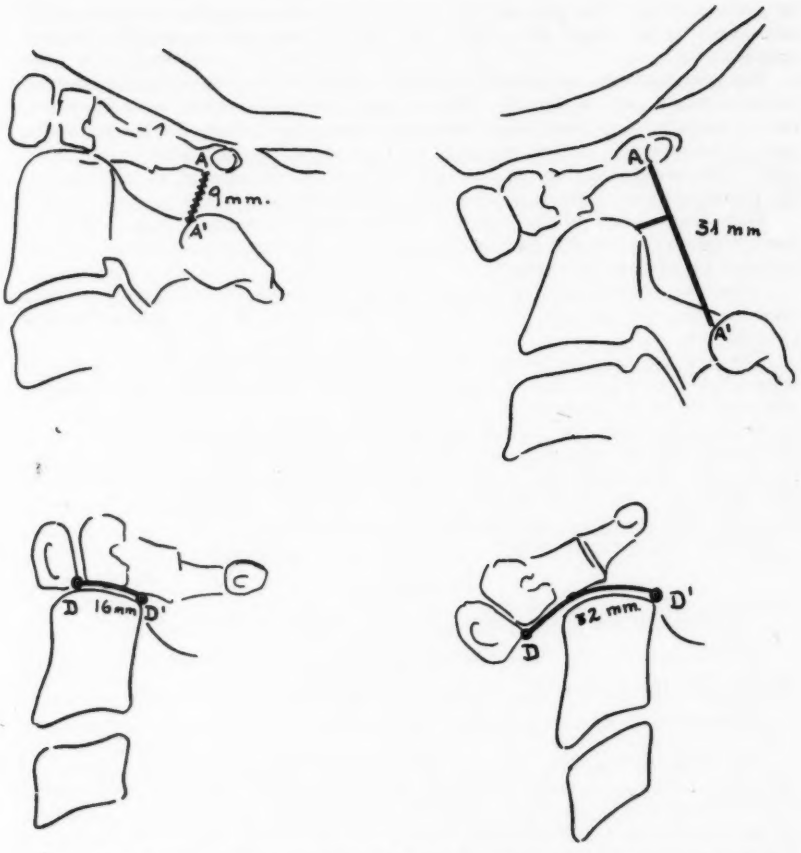

FIG. 6.—Schematic representation of the osteoarticular displacements in the sagittal plane.

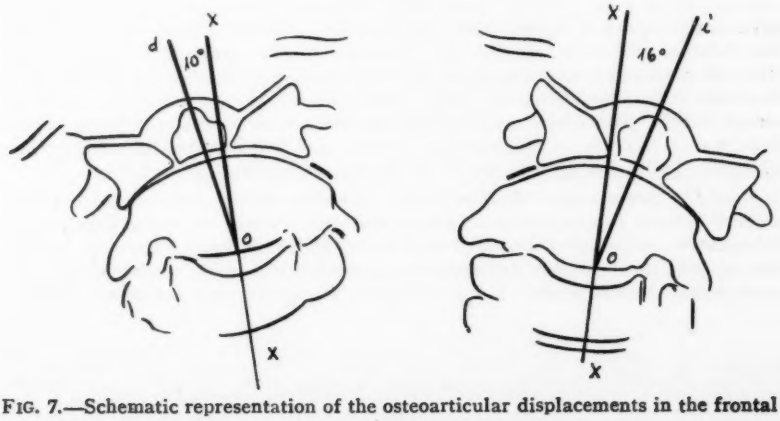

FIG. 7.—Schematic representation of the osteoarticular displacements in the frontal plane.

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the laminæ of the atlas and the axis on each side of the mid-line. During this procedure, spontaneous respiration was temporarily interrupted on several occasions.

The neck was then moderately extended, approximating the posterior arch of the atlas to the arch of the axis. On the right side the vertebræ were fixed with one of the wires. A small tibial bone graft was placed from the lamina of the axis to the posterior arch of the atlas and maintained in position with the other wire. The same procedure was carried out on the left, so that on each side of the spinous process there was a bone graft and two wire loops.

Following closure of the wound a plaster cast was applied maintaining the head in extension. At this moment appnœa recurred. Respiratory stimulants and artificial respiration were needed.

When the patient recovered from the anæsthetic the tetraparesis was more intense. He was able to move only the left limbs. But he was alert and co-operative.

The post-operative course was stormy. Oxygen was given by a mask. Fluids were administered by a Levine tube. On the third post-operative day respiratory difficulty led to performance of a tracheotomy.

On the sixth day the patient had acute hyperthermia, tachycardia, dyspnœa and finally apnœa. On this point the hibernation therapy was begun following the Laborit (1951) technique, and artificial respiration instituted. Improvement was dramatic. He maintained an excellent vegetative function for twenty-two hours but then suddenly irreversible apnœa appeared.

Autopsy was not permitted.

Discussion

Review of Reported Cases of Delayed Myelopathy

We could find in the literature 9 cases in addition to our own (Barraquer-Bordas *et al.*, 1953) of this type, having a neurological asymptomatic interval exceeding one year.

Case I (Grabarz, 1932).—A man aged 36, had persistent physical signs and symptoms following a cervical injury. It was not until two years had elapsed that he began to develop high spinal cord symptoms. X-rays showed a fracture of the body of the axis with dislocation and destruction of the odontoid process. There was forward sliding of the atlas and skull. The author considered that in addition to the trauma there existed an inflammatory factor with pachymeningitis.

Case II (Schwarz and Wigton, 1937).—Man 34 years old. At the age of 10 years this man was injured resulting in unconsciousness and stiff neck. Some days later an articular "crack" was noticed during a movement of the head. When 28 years old a tetraparesis began, most marked in the lower limbs than in the upper with a predominance in the right side. A lumbar puncture yielded a normal C.S.F. There was a partial block in the Queckenstedt test. Radiologically there was a fracture of the odontoid process with a forward dislocation of the atlas and skull. Eight years later the clinical picture was unchanged.

Case III (Schwarz and Wigton, 1937).—A woman 53 years old stated that she had fallen from a horse five years previously. She fainted twice and complained of headache for several days. For four years she was free of symptoms. At the age of 52 slow spastic tetraparesis appeared gradually, accompanied by paræsthesiæ in both hands. C.S.F. : Protein 44 mg. per cent. When a lumbar

encephalogram was attempted a high cervical block was discovered. Radiologically there was a fracture of the odontoid process without displacement. The head was carried in a position of hyperextension tilted to one side. Surgical procedure: laminectomy of the first and second cervical vertebræ revealed no C.S.F. block. Thickening of the dura and milky arachnoid were observed. The spinal cord was normal. The patient improved slightly after operation.

Case IV (Alajouanine, Thurel and Papaioanou, 1949).—A man 47 years old complained of progressive hemiplegia since he was 33 years old. There were sensory alterations, the deep sensibility being affected on the left side and the touch pain and temperature on the right.

The patient complained of sensations like an electric discharge in the left side of the body when the neck was flexed. At the radiological study an atlanto-axial dislocation was found. There was absence of odontoid process. For this reason the case was considered as a congenital malformation. They say: "As there is no record of previous trauma and the odontoid process is absent, it is logical to presume that the disease is due to a congenital malformation, although a trauma cannot be excluded. It is not necessary that there should have been an important trauma to dislocate the atlanto-axoid articulation, and if it has occurred it may have been forgotten fourteen years later. The absence of the dens could be explained then as a reabsorptive phenomenon."

Therefore, this case led us to consider a congenital basis in some cases of atlanto-axoid dislocation. We shall see later that in some patients it is very difficult to say if the disease has a traumatic or congenital ætiology as in many cases the trauma is forgotten, owing to the fact that the neurological symptoms appear so late.

Case V (Macken and Martin, 1949).—A woman 58 years old fell backwards when she was 40. There was contusion of the back of the neck. She was asymptomatic during fourteen years and almost forgot the injury. When she was 54, progressive spastic tetraparesis appeared, the defect being more intense on the left side. There were alterations in sensibility in the four limbs and amyotrophy of the muscles of both hands.

The radiological study showed a fracture of the odontoid process. The dens was displaced forward caught between the anterior arch of the atlas and the body of the axis. There was a dislocation between the atlas and the axis. The atlas produced an abnormal protrusion in the posterior wall of the pharynx.

The patient died at 58. At the autopsy an atlanto-axial dislocation was found. The odontoid process was fractured and fragmented. There were spinal cord lesions, the most important ones being: demyelination, glial reaction and vascular and mesenchymal reaction. The grey matter was also affected. The dura and pia-arachnoid, blood vessels and roots were also altered. The pia-mater and arachnoid were thick, hyaline, richly vascularized and without inflammatory infiltrations. The spinal cord arteries were included but their lumens were still open. The authors stress several points: The anatomical correspondence between the bone deformities and the myelopathy and the alterations observed in the three meninges. They assume that these alterations have a great importance in the pathogenesis of the myelopathy.

Case VI (Barraquer-Bordas, Barraquer-Ferré, Durán, Modolell, Tolosa, Torruella-Pausas and Segarra-Obiol, 1953).—A 28-year-old woman stated that she had fallen from a donkey when she was 5. For some days she had intense pain in the cervical region, and since then she complained of pain of moderate intensity in the back of the neck from time to time. After the trauma she carried the head somewhat flexed.

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During infancy and childhood she had sphincter weakness.

After an unknown febrile disease when she was 28 years old progressive spastic tetraparesis appeared. There were sensory alterations in the four limbs and sphincter disturbances. When the head was flexed there were alterations in the tonus of the arms with a tendency toward flexion. A bony protrusion was observed in the back of the neck.

The X-ray films showed a fracture with fragmentation of the odontoid process, forward dislocation of the atlas producing an abnormal protrusion in the shadow of the pharynx, abnormal position of the spinous process of the axis corresponding to the hard protrusion observed by palpation.

When the head was flexed the atlanto-axial dislocation was aggravated.

A surgical operation was attempted but previous respiratory trouble resulted in interruption of the procedure. Following a stormy forty-eight hour post-operative course the woman died.

Autopsy.—The occipitocervical region was resected in a block. The spinal cord compressed by the bone structures measured only 3 mm. in the A.P. diameter (fig. 5).

The microscopical study showed disintegration in the columns of the spinal cord with intense microglial reaction. Notwithstanding, the ganglion cells had a normal morphology at the same level. The meninges presented a great thickening and the vessel walls were hyperplastic.

Paillas, Legre, Pellegrin and Bonnal (1955) report two cases of chronic and delayed cervical myelopathy following atlanto-axial dislocation by fracture of the odontoid process.

Case VII.—The first patient was a woman, 31 years of age. The original injury occurred at the age of 12 years and a symptom-free period lasted 16 years. The spinal syndrome developed after a new injury. There was a dislocation backwards of the atlas over the axis, so that the anterior arch of the atlas came to occupy the place of the odontoid apophysis. The latter was displaced backwards. A laminectomy was performed, and later a bone grafting, the patient being considerably improved.

Case VIII.—The second patient was a man, 54 year of age. The original trauma took place at the age of 10 years. The symptom-free period lasted 38 years. The development of symptoms followed a new injury. There was a dislocation forward of the occipital bone in relation to the atlas, a dislocation of the atlas backwards, and a lateral dislocation to the right of the odontoid apophysis. A laminectomy was performed followed by bone grafting. The patient improved a little.

The authors point out the complexity of the pathogenesis of the spinal lesions, and discuss the surgical treatment.

Case IX (Salvini and Pelliccioli, 1955).—A man 50 years of age, who was injured at the age of 18 years, was free from symptoms for thirty years. The spinal syndrome was accompanied by painful discomfort and cervical physical signs. The occipital bone and the atlas were dislocated forwards in relation to the axis. The patient improved considerably after radiotherapy directed on the cervical column (900 r by daily sessions of 100 r each). The authors comment on this good result obtained without the necessity of a surgical intervention. They discuss the possible intervention in some of these cases, e.g. the case of Barraquer-Bordas *et al.*, of an inflammatory or infectious factor.

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Characteristics of the Reported Cases

We have found in the literature 9 cases of delayed cervical myelopathy (interval free of symptoms exceeding one year) subsequent to atlanto-axial dislocation produced by a displaced odontoid process. The case herein reported makes a total of 10 observations.

The patient of Alajouanine, Thurel and Papaioanou (1949) is the only one giving no history of trauma. This is probably an instance of congenital agenesia of the odontoid process. But from osteoarticular and neurological point of view it does not differ from the other reported cases.

Case III (Case II of Schwarz and Wigton, 1937) is the only one of this series that did not have forward dislocation of the atlas. In this case the head was displaced towards one side and backwards.

From the neurological point of view the patient presented signs of a cervical myelopathy, having progressive tetraparesis and sensibility alteration.

Case V (Macken and Martin's, 1939) Cases presented pains and muscle atrophies in both arms. These amyotrophies resemble the ones seen in cases of basilar impression as we observed in one of our observations of this deformity (Barraquer-Ferré and Barraquer-Bordas, 1949).

On the other hand, our present patient presented an atrophy of the sterno-cleido-mastoid muscle probably due to a lesion of the accessory nerve.

In our previous case (Case VI, Barraquer-Bordas *et al.*, 1953) we observed modifications in the position of the upper limbs when the neck was moved.

Physical signs in the neck were clearly noticed in our patients. After review of the literature it is not possible to assume that these signs are constant, but probably they were not always accurately investigated.

The pathogenesis of the myelopathy will be discussed later with the analysis of the X-ray study of our 2 cases, and the anatomical data brought for the cases of Macken and Martin and Barraquer-Bordas and co-workers.

We would like to insist here on one of the fundamental characteristics of the disease. It is the existence of a free or almost free interval exceeding one year. This delay was of 2 years in Case I (Grabarz); 4 in Case III (Schwarz and Wigton); 14 in Case V (Macken and Martin); 18 in Case II (Schwarz and Wigton); 23 in Case VI (Barraquer-Bordas and co-workers) and 37 in the present case.

If we admit that the Alajouanine case was congenital we need to accept an interval free of symptoms of thirty-three years.

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Schwarz and Wigton (1937) cited some other cases of similar delayed myelopathy. But all of them presented a free interval of less than eight months. For this reason we exclude them from this review.

McRae (1953) has studied from the radiological point of view cases with bone anomalies of the region of the foramen magnum. Eleven out of one hundred cases, presented "an odontoid process separated from the axis." 8 of the 11 had neurological symptoms. Unfortunately, the author does not give clinical data of the individual patients and it has not been possible for us to include them in our review.

The data in 2 of the cases of McRae are worth mentioning. One, an 18-year-old boy, had had four attacks of an electric shock-like sensation all over the body with temporary quadriplegia brought on by sudden strain. The first three attacks had lasted only a few seconds but the last one was of one hour duration. The other patient of McRae, a 57-year-old farmer, had been having similar sensations over the body with momentary quadriplegia for fifty years. Three days before admission he had bumped his head on the roof of a car and became quadriplegic but not unconscious. It is very interesting to note this long prodromal period of fifty years before definite quadriplegia began.

Characteristics of the reported case and discussion of the pathogenesis of the myelopathy

In the present case there is a history of trauma aggravated by the following factors: the initial injury was severe—a horse kick in frontal region that probably produced a hyperextension of the head. The trauma was repeated fourteen days later with the same result when the wound was broken open.

We think that the trauma has a real ætiological significance in this case in spite of the long interval before the myelopathy began. We know from the study of other cases that a long interval free of neurological symptoms after the trauma is common. This patient has the longest interval of all. For this reason the expression we used in our former paper "delayed myelopathy" is appropriate here also.

In McRae's 11 cases of detached odontoid process of the axis there were only 2 congenital abnormalities. Both were found incidentally; one in a 9-year-old boy who had had a head injury and the other in a 7-year-old epileptic boy. In both cases the odontoid was fused to the anterior lip of the foramen magnum but did not encroach on it. This morphogenetic anomaly supports the congenital ætiology in these cases.

Among the other 9 cases there was a history of trauma in 4. "One of the patients had a severe neck injury in childhood. 3 others had had

severe head injuries thirty, twenty-three and three years before the recent symptoms began, but on direct questioning denied that the neck had been painful or stiff at the time of the head injury."

We know that the existence of a free interval of three, twenty-three and thirty years is not sufficient to exclude the traumatic ætiology but the absence of any neck symptoms at the time of the head trauma is noteworthy, though it is not possible to deny trauma as an ætiological factor.

The other 5 cases of McRae did not reveal a trauma in the history. As Alajouanine, Thurel and Papaioanou (1949) point out, it is possible that the patient fails to recall the injury.

The case of the 9-year-old boy reported by McRae demonstrates that trauma may be a coincidence and the real ætiology a congenital abnormality.

The difficulties in making an ætiological diagnosis in certain cases are such that McRae says: "I do not think it is possible to decide in adults whether we are dealing with an old ununited fracture of the odontoid or an anomaly." Without denying the existence of these difficulties, which we fully recognize, we think that in certain cases, as the present one, the traumatic antecedent may be accepted as a reliable ætiological factor.

Case VI of the total series (Barraquer-Bordas *et al.*, 1953) is a very good example. The history of the patient's neck symptoms after the trauma supports this assertion.

A different point of interest is illustrated by a paper by Grinker and Guy (1927), who reported a patient who had a cervical luxation after minor traumatism: It was a boy who, stretching his arms in the morning felt a pain and stiffness of the neck; one hour later appeared paresis of the arms and twenty minutes later paraplegia and irreversible respiratory troubles. In the autopsy was found thrombosis of the anterior spinal artery; the authors deduced that a momentary cervical luxation occurred.

In our case, as the trauma was produced at the age of 2 years, and the union of the dens is not completed until the 3rd year of age and sometimes later Schinz (1953) we considered our case as an apophysiolysis and not a true fracture.

The facts we have analysed may be summarized as follows:

In the cases of delayed myelopathy by atlanto-axial dislocation due to absence of the normal fixation by the odontoid process, the ætiology may be:

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(A) *Trauma*—in two ways:

(1) By fracture of the odontoid process. This occurred in our first case (Barraquer-Bordas *et al.*, 1953), in the observation of Grabarz (1933), in the 2 cases of Schwarz and Wigton (1937) and in the patient of Macken and Martin (1949). Some of the cases of McRae could be included here.

(2) By apophysiolysis as happened in our present case.

(B) *Congenital malformation*—of two types:

(1) Congenital absence of odontoid process; as probably occurred in the case of Alajouanine *et al.*, (1949).

(2) An anomaly of union of the odontoid process due to a congenital anomaly. Probably more than one of the cases of McRae (1953) with neurological symptoms have this ætiology. In 2 cases this ætiology was certain, because a malformation was present (union of odontoid process with the anterior lip of foramen magnum). But it is peculiar that in those 2 cases there were no neurological symptoms.

The pathogenesis of the myelopathy associated with our type of atlanto-axia dislocation may be better understood after the radiological study of our two cases, and of the anatomical findings brought out by our first case and the case of Macken and Martin.

From the radiological point of view it is necessary to make a sharp distinction between two processes:

(*a*) The simple atlanto-axial dislocation.

(*b*) The atlanto-axial dislocation by fracture, apophysiolysis, defect of union or aplasia of the odontoid process.

In the dislocation by fracture or apophysiolysis the transverse ligament remains intact. In the simple atlanto-axial luxation, on the other hand, this ligament is torn out allowing the dislocation. There exist cases of simple atlanto-axial dislocation of congenital origin. McRae, out of 6 cases, finds 3 with a probable congenital basis.

A different physiopathological status results from the two processes, there being differences in the frequency and intensity of involvement of the nervous structures. This fact may be estimated by further examining McRae's (1953) paper. The neurological symptoms were more severe and frequent in the cases with separated odontoid process.

In the simple atlanto-axial luxation there exists a slipping (usually moderate) between atlas and axis in two parellel planes. When the head is flexed the abnormal mobility between skull-atlas and axis is reduced to a minimum, the flexion being made in the middle and lower cervical vertebræ (McRae, 1953).

The atlanto-axial dislocation by separated odontoid process is, con-

versely, characterized by an intense abnormal "patellar" mobility that the skull-atlas has on the convex surface of the axis body. When the head is flexed the dislocation between atlas and axis is in comparison to that occurring in the simple atlanto-axial luxation more impressive. Furthermore, the luxation does not follow two parallel planes, because the atlas luxates forward and downwards. The dislocation "plane of the atlas" makes with the "plane of the axis" a progressive angle open upwards and backwards.

As we said before, after a fracture of the odontoid process there exists another abnormal movement of an atlas slipping in a transverse plane. The dens being fixed by the transverse ligament follows the displacements of the atlas.

McRae measured in his cases the amount of the slipping of the atlas on the axis. In the three cases of simple atlanto-axial luxation whose measurements were taken the slipping was minimum (from 0·3–4 mm.). But in the cases of a separated odontoid process the slipping measured from 5 to 25 mm. (average 14 mm. in the symptomatic cases and 10 mm. in the asymptomatic cases). Though it is impossible to establish comparisons between different X-ray plates as the figures vary depending on several factors, in our case the displacement measured in the film taken with a safe moderate flexion of the head was 16 mm. We insisted in our previous paper on the necessity of careful positioning of the head during a radiological examination to avoid injury of the cord.

As a consequence of the peculiar displacement of the atlas on the axis after atlanto-axial dislocation by fracture, etc., of the odontoid process, there appears a great separation between the spinous processes of the first and second cervical vertebræ. In our patient during head extension the distance between the spinous processes was 9 mm. When the head was flexed the separation increased till measuring 31 mm. This separation must produce a stretching of the dura mater and ligaments against which the spinal cord is crushed when pushed by the axis body.

The anatomical specimens of our first patient reproduced here (fig. 5) show it clearly. At this level there is the point of maximum compression, the A.P. diameter of the veretbral canal being only 3 mm.

In our present case we measured a similar distance by drawing on the X-ray plate a line joining the internal surfaces of both posterior arches, and then drawing a perpendicular to this line from the most prominent point of the body of the axis, the head being in flexion. This line measured 5 mm.

McRae in cases of occipitalization of the atlas measured the A.P. diameter of the vertebral canal taking the distance between the displaced

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dens and the posterior margin of the foramen magnum. In McRae's cases when the A.P. diameter was 19 mm. or less, neurological symptoms appeared.

In McRae's series of simple atlanto-axial luxation (6 cases) the depth of the spinal canal behind the dens was from 8–20 mm. with an average of 15 mm. In only 3 cases did neurological symptoms appear.

In our two observations the narrower point of the spinal canal was limited posteriorly by soft tissues.

In the case of Macken and Martin as the odontoid process was displaced the greater compression occurred at the level of the arch of the atlas. In this case the spinal cord was obliged to follow in the spinal canal a bayonet course, with a first angle open downwards and forward, in front of the superior fragment of the dens, and a second angle open downwards and backwards in front of the posterior arch of the atlas. This disposition is quite different from the one observed in our two cases, the spinal cord bending over the body of the axis.

In fig. 6 we reproduce the displacements and angles mentioned.

We wish to insist now on the lateral displacements of the atlas on the axis, as no attention has been given before to this abnormal mobility. The odontoid follows the atlas moving in a pendular fashion (fig. 7). It is possible that it scrapes the anterior aspect of the spinal cord which is compressed at the same time at each side by the lateral masses of the axis.

In the lateral X-ray plates there may be observed in our present case, as in our earlier observation, the protrusion of the spinal process of the axis in the neck and the high position of the anterior arch of atlas in the pharynx. This detail was also described by Macken and Martin in their case.

In this discussion we have established the differences between two processes: The simple atlanto-axial luxation and the luxation after fracture, etc., of the odontoid process. We must now mention the existence of a third type of articular abnormality: The posterior subluxation of the odontoid process, which is frequently found in cases of congenital abnormalities in the region of the foramen magnum, especially in cases of assimilation of the atlas. The odontoid process appears displaced from its normal relationship. The ligaments are hypoplastic and permit the posterior displacement of the dens when the head is flexed.

The first author to stress the importance of this posterior subluxation of the odontoid in the pathogenesis of the associate myelopathy was List (1941). In one of our cases of basilar impression (Barraquer-Ferré

and Barraquer-Bordas, 1941) there existed a posterior subluxation of the odontoid probably responsible for the spinal symptoms.

Later the Lyon's school insisted on the relation of this posterior subluxation of the odontoid process to the myelopathies associated with malformations of the occipito-vertebral region. An important anatomical and clinical instance was reported by Ricard, Girard, Bonnet and Replumaz (1949). They assume that the joint lesions resulting from abnormalities in the occipito-vertebral region could in some cases be responsible for the dislocation.

MacRae also (1953) describing the atlas assimilation makes reference to the posterior subluxation of the dens. This author says: "If the odontoid process moves back and forth more than 3 mm. in flexion and extension of the head, neurological signs always occur," and, later: "In the two cases of occipitalization of the atlas that came to autopsy there was a depression in the anterior surface of the medulla oblongata into which the odontoid projected."

The congenital bone pathology in the cervico-occipital region has been extensively reviewed in the recent monograph by Garcin and Oeconomos (1953).

Going back to the pathogenesis of the myelopathy in the cases of atlanto-axial dislocation by fracture, etc., of odontoid, we must point out again the exact correspondence between the transverse myelopathy and the bony alterations. In the two anatomical examples of the literature, the cases of Macken and Martin and of Barraquer-Bordas *et al.*, the spinal cord softening was extreme at the level of the narrower point of the vertebral canal. Compression, angulation and stretching of the spinal cord, depending on the osteoarticular pathology, are important causal factors of the myelopathy. Which are the intermediate processes between these osteo-articular factors and the myelopathy?

To answer this question it is necessary to bear in mind two significant points. First, the mobility of the bone structures shows that the compressive factors are not constant; though it represents an intermittent friction and stretching having great pathogenetic importance. On the other hand, the existance of a symptom-free interval indicates that the odontoid fracture produces the myelopathy through a chain of several links, some of them of very slow elaboration.

The anatomical studies of Macken and Martin and Barraquer-Bordas *et al.*, illuminate some of these links. In both cases the histopathological findings of an alteration and thickening of the three meninges and modifications in the blood vessels are conspicuous.

The importance of a vascular factor in the pathogenesis of the myelo-

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pathy depending on the bony pathology of the occipito-cervical region has been pointed out by a great deal of authors. Some of these vascular alterations produce a spinal cord lesion whose clinical representation is a syringomyelic syndrome. This problem is a very interesting one as the genuine syringomyelia may coexist with congenital abnormalities of the same region. Roger and Marcorelles (1942) and Barraquer-Ferré and Barraquer-Bordas (1945 *a* and *b*) reviewed the literature and published their own cases.

Lichtenstein (1943) published a paper on the study of cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platubasia. He classified alterations of several types. Subsequent information on this problem may be obtained from the paper of Barraquer-Bordas (1949) and in the monograph of Garcin and Oeconomos (1953).

Treatment

For the surgical treatment of our case we planned an osteosynthesis. The operation was based on a modification of Guillaume and Lubin's technique (1941), which consists in passing wires below the posterior arch of the atlas fixing them in the occipital squama and the spinous process of the axis. It avoids the forward displacement of the atlas. Guillaume (1952) says the results are good in simple atlanto-axial dislocation.

In our case we tried to abolish the abnormal mobility of the atlas not only in the anteroposterior plane but also in the frontal plane. We fixed the wires as described above and also inserted a bone graft. We did not consider it necessary to fix the occipito-atloid articulation.

We experienced the dangers of this technique and we think it may be safer to practise only an occipito-cervical fusion with a bone graft and immobilization. It will be useful to practise such operations with the head extended with the Crutchfield tongs. It is of great importance to maintain the head in a straight position during operation. In fact, in our 2 patients not only flexion of the head but also extension impaired the respiration. The middle position was the best tolerated.

The increase in the symptoms with head extension could be due to the compression produced by the posterior soft tissues between the atlas and axis bulging forward in this position.

List (1941) and especially Ricard *et al.* (1949) used bone grafts in the operative treatment of their cases of congenital cervico-occipital pathology with posterior subluxation of the odontoid extending the graft to the occipital bone.

In only one of the reviewed cases was a laminectomy done. This was Case III of Schwarz and Wigton. This patient had a posterior luxation of the head. Frazier carried out a laminectomy of the atlas and axis. He reported a thickening of the dura mater and arachnoid, this last membrane having a milky appearance. This finding corroborates the data derived from the anatomical studies of Cases V (the case of Macken and Martin) and VI (the case of Barraquer-Bordas *et al.*). After laminectomy the patient improved for some time and finally maintained a stationary course. We do not think that a radiotherapic treatment may benefit these patients, in spite of the results reported by Grabarz.

It is advantageous before embarking on the surgical treatment of one of these patients to study the case carefully from the radiological point of view practising tomography, etc.

The conclusion to be drawn from this and our previous case is the same which Macken and Martin drew from their work—after a neck injury it is necessary to practise a complete radiological study of the region; this would render possible early treatment and prevent the myelopathy, the pathology of which makes it difficult to obtain a real benefit from operation once it is established.

Summary

The authors describe the second case observed at the Neurological Clinic of the Hospital de la Sta. Cruz y S. Pablo, of Barcelona, of delayed myelopathy after atlanto-axial luxation by a separated odontoid process.

The literature contains only 9 cases of this delayed myelopathy, including their own first case.

After summarizing the present case they discuss some of the characteristics of the condition. The great duration of the interval free of symptoms is emphasized.

The differences between the simple atlanto-axial luxation and the dislocation after fracture, etc., of the odontoid process, were discussed.

From the cases found in the literature, the two observations of the authors, and those briefly reported by McRae, it is concluded that the ætiology of the atlanto-axial luxations of the last type includes four possibilities: fracture of the odontoid process, apophysiolysis, aplasia of the dens and defective union of the dens due to a congenital alteration.

The anatomical findings of the cases of Macken and Martin and Barraquer-Bordas *et al.* are reviewed to show the topographical correspondence between the transverse myelopathy and the bony alterations.

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It is concluded that the slow intermittent progressive action of the compression, angulation and stretching of the spinal cord produced by the osteoarticular pathology lead to the delayed myelopathy. In the pathogenesis of the myelopathy, important factors are the blood vessel alterations and the hypertrophic meningopathy.

The treatment and the prophylaxis of the condition are also discussed.

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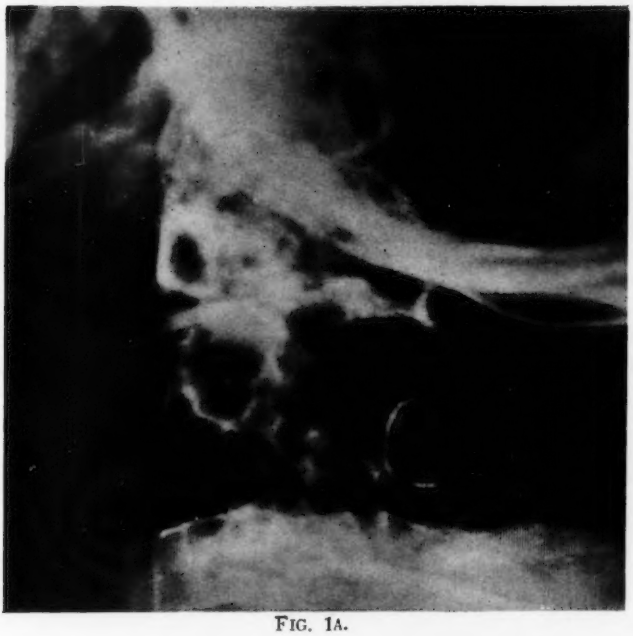

FIG. 1A.

FIG. 1B.

To illustrate article by Bachs, Barraquer-Bordas, Barraquer-Ferré, Canadell, Modolell

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PLATE XLVIII

FIG. 2.

To illustrate article by Bachs, Barraquer-Bordas, Barraquer-Ferré, Canadell, Modolell

PLATE XLIX

FIG. 3.

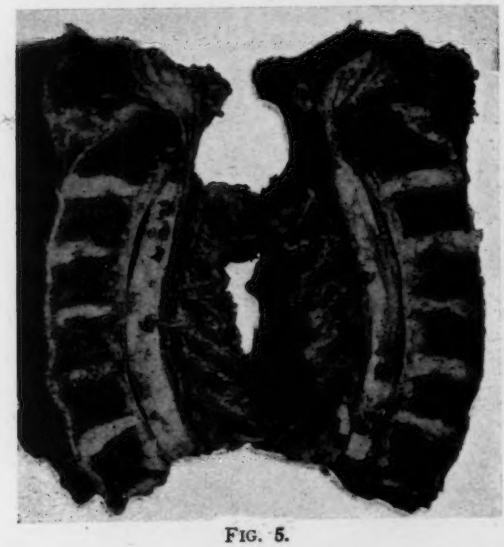

FIG. 5.

To illustrate article by Bachs, Barraquer-Bordas, Barraquer-Ferré, Canadell, Modolell

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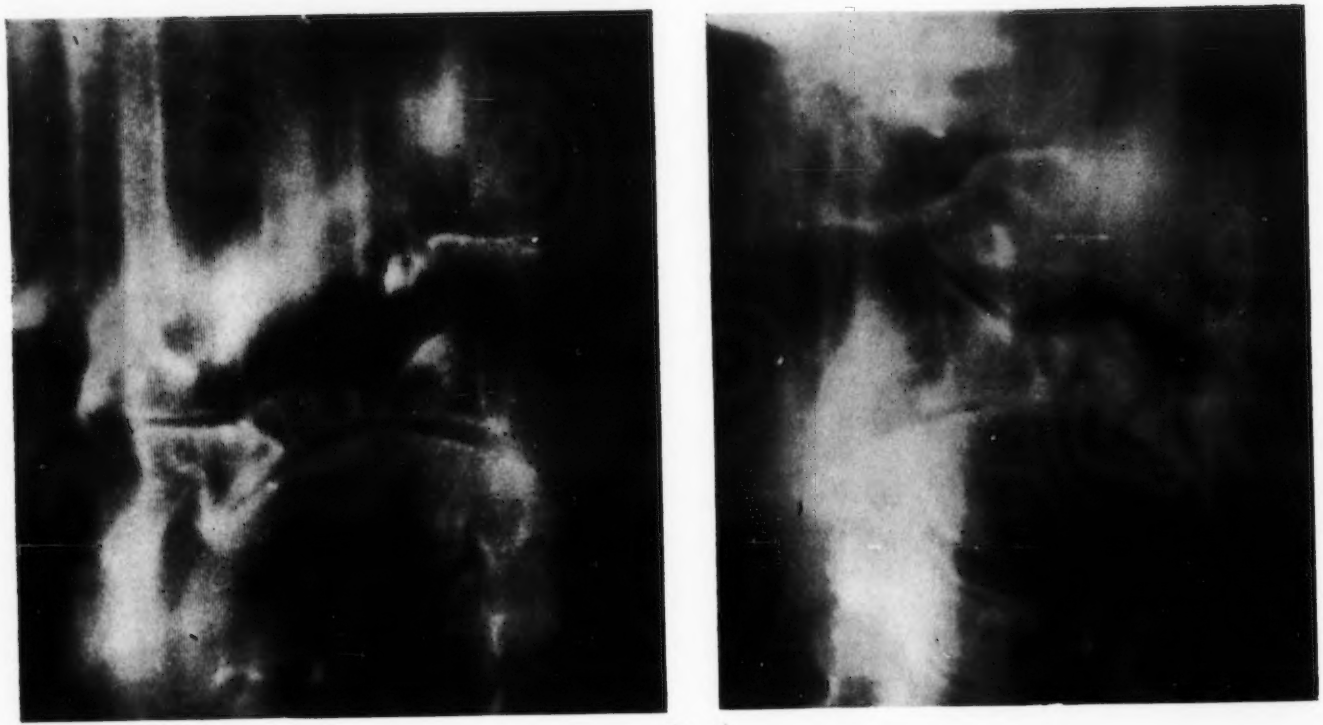

FIG. 4.

To illustrate article by Bachs, Barraquer-Bordas, Barraquer-Ferré, Canadell, Modolell

LEGENDS TO PLATES

PLATE XLVII

FIG. 1A.—Lateral view. Extension.

FIG. 1B.—Lateral view. Flexion.

PLATE XLVIII

FIG. 2.—Lateral tomographic view. Left, flexion. Right, extension.

PLATE XLIX

FIG. 3.—Frontal tomographic view. Middle position.

FIG. 5.—Necropsy specimen of our previous case (Barraquer-Bordas *et al*).

PLATE L

FIG. 4.—Frontal tomographic view, during inclination of the head to left and to right.

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LIPID CHEMISTRY OF THE BRAIN IN DEMYELINATING DISEASES

BY

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CERTAIN changes in the lipid pattern of the brain in multiple sclerosis and in the sudanophilic type of diffuse cerebral sclerosis have recently been described (Cumings, 1953). It was found that in 2 cases of the former condition there was a diminution of phospholipids with the presence of cholesterol esters in the demyelinated areas in the cerebral white matter. The apparently normal areas of the brain were also shown to be slightly abnormal. The changes in the case of diffuse sclerosis were very similar to those seen in the cases of multiple sclerosis.

Similar investigations in 3 new cases of multiple sclerosis, one case of sudanophilic diffuse sclerosis and in one case of metachromatic diffuse sclerosis have been performed and this paper records the results obtained, together with other investigations into these cases and other types of lipidosis.

MATERIAL

Portions of grey and white matter were obtained from cases of multiple sclerosis, various forms of diffuse sclerosis, amaurotic family idiocy, normal adults and normal newborn babies after the brains had been fixed in formol-saline for two weeks, it having already been demonstrated that this treatment did not affect the results of such phospholipid examinations as had previously been made. A few brains were also examined in the fresh state and this is indicated in the appropriate places in the tables.

METHODS

Water content, total phospholipid, mono-amino phospholipid, sphingomyelin, lecithin, cephalin, cholesterol and cerebroside were estimated as already described (Cumings, 1953). Extraction of the

phospholipids was performed with a hot alcohol-ether mixture on each occasion.

Neuraminic acid was estimated as described by Klenk and Langerbeins (1941) except that the colour was developed at 100° C for fifteen minutes as described by Böhm, Dauber and Baumeister (1954).

The cerebral material was prepared for estimations of acid-soluble phosphorus, phospholipid phosphorus, nucleic acid phosphorus and phosphoprotein phosphorus by the method of Schneider (1945) and the phosphorus content of each of these four groups of substances was estimated by the method of Fiske and Subbarow (1925).

Neutral fat was estimated by the method of Voris, Ellis and Maynard (1940).

Results

The lipid contents in the 3 cases of multiple sclerosis are shown in Table I from which it is seen that in 2 of the cases there is a well-marked fall in the total phospholipid concentration and that cholesterol esters are present in the demyelinated areas of the white matter. There is a somewhat lowered phospholipid content together with the presence of cholesterol esters in the so-called normal areas of the white matter in these same cases. The normal areas were chosen because they showed no macroscopic abnormality. The cerebral cortex is normal except over the demyelinated plaques, where some loss of phospholipids is apparent. These findings are similar to those previously described.

The third case was that of an elderly man who had suffered from his disorder for many years and the cerebral demyelinated plaques were few in number and small in size. These plaques show some loss of phospholipids but no cholesterol esters are present even though the total cholesterol is lower than normal. The macroscopically normal white matter and the cerebral cortex in all areas are normal chemically.

Table II shows the results of a series of similar examinations in a case of sudanophilic and in a case of metachromatic diffuse sclerosis.

The sudanophilic type of diffuse sclerosis was found in a young girl of 14 years with an acute illness of only a few months' duration. It is seen that the normal cerebral white matter showed no chemical abnormality. The demyelinated area, which was partly cystic and from which fluid was obtained, shows an extreme loss of phospholipids with the presence of a very considerable amount of cholesterol esters. The cerebral cortex and the basal ganglia are not chemically abnormal.

The cyst fluid from the case is seen to contain a relatively large amount of phospholipids but no cholesterol at all.

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TABLE I.—LIPID CONTENT IN MULTIPLE SCLEROSIS
(*Brains Fixed in Formalin for Two Weeks*)

Case	*Portion of brain*	*Total phospholipid*	*Monoaminophospholipid*	*Sphingomyelin*	*Lecithin*	*Cephalin*	*Total cholesterol*	*Free cholesterol*	*Cerebroside*	*Water*
No. 51036 ..	Cerebral white (normal)	5·5	2·7	2·8	1·3	1·4	3·8	3·5	5·01	66·7
	Cerebral white (demyelinated)	3·0	2·46	0·54	1·24	1·22	2·57	1·71	1·14	82·3
	Cerebral cortex (normal)	3·9	2·5	1·4	1·1	1·4	1·5	1·5	1·35	78·8
F 56	Cerebral cortex (over demyelinated area) ..	2·85	1·93	0·92	0·54	1·39	1·28	1·21	0·34	
	Cerebral white (normal)	4·22	2·44	1·78	0·89	1·55	3·63	2·56	5·2	77·2
No. 49733 ..	Cerebral white (demyelinated)	2·5	1·5	1·0	0·52	0·98	2·25	1·13	1·2	82·2
	Cerebral cortex (normal)	4·06	2·63	1·43	1·08	1·55	2·13	1·99	1·84	84·2
F 54	Cerebral cortex (over demyelinated area) ..	3·59	2·40	1·19	0·84	1·56	1·50	1·44	1·47	83·9
	Cerebral white (normal)	6·56	4·03	2·53	1·39	2·64	4·12	4·0	6·24	69·0
E. M.	Cerebral white (demyelinated)	4·38	2·63	1·75	0·80	1·83	2·25	2·13	3·4	76·3
M.	Cerebral cortex (normal)	3·28	2·34	0·94	0·80	1·54	1·25	1·25	2·1	84·1
	Cerebral cortex (over demyelinated area) ..	3·62	2·48	1·14	0·96	1·52	1·24	1·24	1·46	79·1

All results in g/100 g. wet weight. ..

TABLE II.—LIPID CONTENT IN SUDANOPHILIC AND METACHROMATIC TYPES OF DIFFUSE SCLEROSIS
(*Brains only Fixed in Formalin for Two Weeks*)

	Tissue	*Total phospholipid*	*Monoaminophospholipid*	*Sphingomyelin*	*Lecithin*	*Cephalin*	*Total cholesterol*	*Free cholesterol*	*Cerebroside*	*Water*
Sudanophilic	Cerebral white (normal)	5·63	3·4	2·23	1·58	1·82	3·5	3·25	6·15	75·9
No. 44216	Cerebral white (demyelinated)	0·63	0·58	0·05	0·22	3·81	3·81	0·56	0·99	81·1
F 14	Cerebral cortex	3·12	2·1	1·02	0·98	1·12	1·75	1·50	2·84	85·2
	Basal ganglia	4·5	3·3	1·2	1·54	1·76	3·05	2·84	5·8	76·2
	Results in g./100 g. wet weight									
	Cyst fluid	43·5	32·0	11·5	5·4	26·6	0	0	42·6	
	Results in mg./100 ml.									
	Cerebral white (normal)	4·0	2·5	1·5	1·14	1·36	1·30	1·18	1·56	84·0
Metachromatic	Cerebral white (demyelinated)	3·15	2·0	1·15	0·89	1·11	1·4	1·3	2·23	83·8
No. 37966	Cerebral cortex	3·75	2·03	1·72	0·82	1·21	0·96	0·91	0·45	88·0
	Basal ganglia	3·4	1·77	1·63	0·51	1·26	1·14	1·02	1·52	82·2
F 13	Liver	2·28	1·28	1·0	0·44	0·84	0·24	0·19	1·24	70·0
	Results in g./100 g. wet weight									

The metachromatic type of diffuse sclerosis occurred in a girl of 13, and the histological features of this case were very similar to those described by Norman (1947). The findings as seen in Table II are that all the white matter of the cerebrum was œdematous, and that while the demyelinated zones are the areas more severely affected chemically all parts of the white matter show loss of phospholipid content yet without the presence of cholesterol esters. However, the cerebroside content of the demyelinated areas although very slightly higher than the normal white is definitely lower than normal. The cortex and the basal ganglia are almost normal chemically.

Neuraminic Acid

Recently Professor Klenk has supplied me with some neuraminic acid and it has been possible to estimate the amount of this substance present in the brains not only of the cases just described but also in those previously reported (Cumings, 1953; Blackwood and Cumings, 1954) and in one case of amaurotic family idiocy recently sent me by Dr. Phillips. Table III shows the results obtained on this pathological material and in some normal controls.

Table III.—Neuraminic Acid Content in Brain
(*All Brains Fixed in Formalin Two or More Weeks*)

Case			*Cerebral white matter*	*Cerebral Cortex*
Normal adults			0	140–180
Amaurotic family idiocy		J. P.	(30)	280
		No. 23010	(50)	296
		No. 24516	(40)	320
		No. 16041	(40)	296
		No. 19884	(55)	360
		R. H.	(12)	260
Multiple sclerosis		No. 38103	(25)	280
		No. 36134	0	240
		No. 51036	(80)	230
		No. 49733	(25)	300
		E. M.	(50)	200
Diffuse sclerosis.	Sudanophilic.	Q. C.	(46)	256
	,,	No. 44216	0	375
	Spongy	No. 28860	(80)	310
	Pelizaeus Mersbacher.	E. W.	(110)	280
	Krabbe or Globoid.	No. 21280	(24)	184
	Metachromatic.	No. 37966	(63)	275

All results in mg/100 g. dry tissue.
For explanation of figures in brackets see text.

It is noticed that there is an increased amount of neuraminic acid in the cerebral cortex in all the cases of amaurotic family idiocy but that in 4 of the cases of multiple sclerosis and in those of diffuse sclerosis figures definitely above the normal were obtained. The figures in brackets would be regarded by Klenk and Langerbeins (1941) as representing absence of neuraminic acid for a colour was produced in each of these tests which, while giving a reading, was not the true colour reaction; further, application of the methyl alcohol test of Klenk and Langerbeins showed that the colours were not the result of the presence of neuraminic acid. This colour change may in fact be produced by some other carbohydrate product, and may perhaps be related to a cerebroside, to hexosamine or to some other substance.

A comparison has been made between the actual method used by Klenk and Langerbeins and that followed in this investigation, and apart from the greater convenience of heating for fifteen minutes at 100° C instead of for five minutes at 142° C there was no appreciable difference between the methods, nor in the results obtained.

Table IV shows the results of estimations of some phosphorus-containing substances including nucleic acid and phosphoprotein. As the bulk of the pathological material was examined after two weeks in formalin, normal brains were examined both in the fresh state and after formalin fixation and certain changes were found as a result of this treatment. As can be seen from the table there is a considerable loss of acid-soluble phosphorus during this period, and no doubt the fixing solution extracts this substance. Phospholipid phosphorus and nucleic acid phosphorus change little during this period of fixation.

There appears to be little difference in the quantity of phosphoprotein phosphorus present in the white matter and the cerebral cortex until some weeks after fixation, when the amount in the cortex appears to be somewhat higher than in the central white matter; but there is a general increase of this substance in both areas as a result of formalin fixation. Any variation from the normal found in the pathological material must therefore be substantial before it can be considered significant.

Turning to the pathological material, acid-soluble phosphorus is low but only slightly below the content in the normal fixed material. Phospholipid phosphorus is low in the demyelinated zones as has been shown in the results previously recorded in multiple sclerosis and in diffuse sclerosis (*see* Tables I and II). Nucleic acid phosphorus is slightly increased in all the demyelinating diseases both in the normal and abnormal areas apart from the degenerate white matter in the acute case of sudanophilic diffuse sclerosis, and in the case of the meta-

TABLE IV.—PHOSPHORUS CONTAINING SUBSTANCES IN CEREBRAL WHITE AND CEREBRAL CORTEX

Disease	Case	Fresh or fixed	Acid soluble P	Phospho-lipid P	Nucleic acid P	Phospho-protein P	Water
Normal:							
White: One week old infant		Fresh	760	155	74	90	87·7
,, Adult		,,	310	630	54	80	67·3
,, ,,		Formalin 1/52	112	662	78	210	67·3
,, ,,		,, 4/52	195	335	74	230	67·3
Cortex: One week old infant		Fresh	740	155	124	90	90·4
,, Adult		,,	410	450	60	80	82·4
,, ,,		Formalin 1/52	80	510	64	210	82·4
,, ,,		,, 4/52	255	205	124	310	82·4
Multiple Sclerosis:							
White: Normal area	38103	Formalin 2/52	100	290	96	290	76·3
,, Demyelinated area	,,	,, ,,	105	235	108	310	81·4
Cortex:	,,	,, ,,	95	255	138	410	84·4
White: Normal area	36134	,, ,,	60	300	94	280	69·0
,, Demyelinated area	,,	,, ,,	55	175	102	170	80·4
Cortex	,,	,, ,,	150	200	136	420	82·5
White: Normal area	49733	,, ,,	50	350	106	260	77·2
,, Demyelinated area	,,	,, ,,	55	284	112	240	82·2
Cortex:	,,	,, ,,	240	140	112	310	84·2
Diffuse Sclerosis:							
(*a*) Sudanophilic							
White: Normal area	44216	,, ,,	195	355	108	240	75·9
,, Demyelinated area	,,	,, ,,	55	75	72	65	81·1
Cortex:	,,	,, ,,	120	275	134	340	85·2
(*b*) Spongy							
White:	28860	,, ,,	115	120	106	220	92·2
Cortex:	,,	,, ,,	110	130	114	280	85·6
(*c*) Pelizaeus Mersbacher							
White:	E.W.	,, ,,	93	128	106	285	84·3
Cortex:	,,	,, ,,	85	155	114	280	82·8
(*d*) Krabbe (Globoid)							
White:	21280	,, ,,	140	120	114	220	84·2
Cortex:	,,	,, ,,	155	200	116	310	84·2
(*e*) Metachromatic							
White: Normal area	37966	,, ,,	43	255	165	267	84·0
,, Demyelinated area	,,	,, ,,	45	240	93	160	83·8
Cortex: Normal area	,,	,, ,,	78	204	101	240	88·0
Amaurotic family idiocy:							
White:	16041	,, ,,	100	400	80	280	65·3
Cortex:	,,	,, ,,	65	300	126	380	80·6

All results in mg. P/100 g. dry tissue.

chromatic type of diffuse sclerosis. This increase in nucleic acid phosphorus may be and probably is the result of a greater cellularity from an increased number of glial cells.

The figures for phosphoprotein phosphorus in the normal white matter are as high as in the normal brain but are actually lower than those found in the cortex. The levels in the demyelinated area are all lower than either of the other two areas, even though formalin-fixed material was utilized throughout. Specially low figures for this substance were obtained in one case of sudanophilic and in the case of

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metachromatic diffuse sclerosis, in fact in the same cases as showed a low nucleic acid phosphorus.

It is of some interest to note the very high figures of acid-soluble phosphorus in the infants brain, for this is present before myelination and this phosphorus is probably readily available for the formation of myelin lipids.

Neutral Fat

Estimations of neutral fat have been made in most of these cases but they do not reveal any significant variations from the normal, and this was in fact rather as expected.

Discussion

The changes found in the phospholipid content of the brain in two of the three cases of multiple sclerosis described here have confirmed my previous findings not only as regards the demyelinated zones but also as regards the relatively normal areas. The third case was of long duration with few cerebral plaques and while these were abnormal chemically the normal areas of the brain showed no abnormal features.

It is significant that the chemical changes found in the cases of sudanophilic diffuse sclerosis parallel those seen in multiple sclerosis, for histologists have held the view that these two conditions are similar, even though the degree of damage in the lesions differs.

The changes found in nucleic acid phosphorus are not unexpected and parallel the histological changes found in demyelinated areas. The low figure found in the sudanophilic diffuse sclerosis can be explained as in this case the changes were of an acute nature and there had not been time for much cell increase, and in fact degenerative cystic changes were found in the cerebral white matter.

Bodian and Dziewiatkowski (1950) and Logan, Mannell and Rossiter (1952*a*) had obtained higher figures of phosphoprotein phosphorus in white matter than in the cortex in animals even though some of this fraction probably includes some "inositide P" as well. The findings described here suggest that in normal fresh human brain there is very little difference between these two areas, although some change takes place after four weeks in formalin.

Logan, Mannell and Rossiter (1952*b*) found that on sectioning nerves there was a steady drop in phosphoprotein phosphorus throughout the whole time of degeneration, but that in a crushed nerve where regeneration took place, although there was at first a drop in phosphoprotein phosphorus yet there was later a return to normal.

The results found in the cases examined here suggest that in the demyelinated areas there was an initial loss of phosphoprotein phosphorus, but that later there had been a return to a more normal level in a manner paralleling that found experimentally in the crushed nerves. This suggestion might be regarded as being confirmed by the low figure found in the case of sudanophilic diffuse sclerosis, and by the figures for the demyelinated areas which are all lower than those of the cerebral cortex. It does seem most desirable that "inositide P" and true phosphoprotein phosphorus be estimated separately, and that these examinations should all be made on fresh tissue.

Klenk and Langerbeins report increased amounts of neuraminic acid in the cortex only in cases of amaurotic family idiocy and, while this has been confirmed, yet raised levels have been found in all forms of demyelinating diseases so far investigated even though normal levels were found in the cerebral cortex of brains from such conditions as Friedreich's ataxia and Gaucher's disease. So far neuraminic acid has not been detected in the white of any brain.

TABLE V.—LIPID ABNORMALITIES IN DEMYELINATING DISEASES

Disease	*Number of cases*	*Total phospho-lipid (white)*	*Cholesterol esters (white)*	*Cerebroside (white)*	*Neuraminic acid (cortex)*	*Phospho-protein phosphorus (white)*	*"Hexo-samine" (White)* (300)
Amaurotic family idiocy	6	Normal or reduced (+)	Absent	Normal or reduced (±)	Increased (++)	Reduced (±)	Increased (±) (330–430)
Multiple sclerosis	5	Reduced (+)	Present (+)	Reduced (+)	Increased (+)	Reduced (+)	Normal or Increased (±) (250–400)
Sudanophilic	2	Reduced (++)	Present (++)	Reduced (++)	Increased (+)	Reduced (++)	Variable (198 and 580)
Spongy	1	Reduced (+++)	Absent	Reduced (+)	Increased (+)	Reduced (±)	Normal for age (500)
Pelizaeus Mersbacher	1	Reduced (+)	Absent	Reduced (++)	Increased (+)	Normal	—
Krabbe or globoid	1	Reduced (++)	Absent	Increased (+)	Normal	Reduced (±)	Normal for age (400)
Metachromatic	1	Reduced (+)	Absent	Reduced (+)	Increased (+)	Reduced (+)	Increased (++) (570)

"Hexosamine" mg./100 gramme dry tissue.

Table V demonstrates the more specific changes found in all these conditions. The suggestion is therefore made that it might be possible with less than 1 gramme of cerebral biopsy material obtained during life to suggest tentatively the diagnosis of any of these cases with the possible exception of the metachromatic type of diffuse sclerosis. Edgar (personal communication) has found that hexosamine levels are raised

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in this condition and we have confirmed this in the white matter in one case.

Further investigations have shown that there is more "hexosamine" in the white matter of brains of young infants as compared with normal adults, so that this fact must be considered when assessing results. The earlier methods employed for estimating "hexosamine" leave much to be desired, and a survey of the methods and the results obtained using modified techniques will be presented later. Meanwhile Table V included an indication of the results so far obtained both as to general increases and also some actual amounts found.

Some difficulty may also arise in distinguishing between multiple sclerosis and the sudanophilic type of diffuse sclerosis.

Recently there occurred the opportunity to examine cerebral biopsy material from a boy of 4. After histological examination had been made the remainder of the tissue weighing less than 0·7 gramme was examined chemically. The results are seen in Table VI.

TABLE VI.—OPERATION SPECIMEN FROM P.B., AGED 4 YEARS
Total weight of biopsy specimen =0·67 gramme

	White	*Grey*
Total phospholipid	6·08	2·93
Cerebroside	2·9	2·6
Total cholesterol	3·3	—
Free ,,	3·2	—
Neuraminic acid	—	275
" Hexosamine "	690	—
Water	81·0	85·6

The features are a normal phospholipid content, no increase of cholesterol esters or cerebroside but increased water, neuraminic acid and "hexosamine" contents. These findings are all compatible with an early stage of lipidosis of the amaurotic family idiocy type in a young child and this finding agrees with the histological diagnosis.

SUMMARY

Phospholipids, cholesterol, various phosphorus-holding compounds, neutral fat and neuraminic acid have been estimated in 3 further cases of multiple sclerosis and 1 of diffuse sclerosis of the sudanophilic type and in other varieties of diffuse sclerosis and these results are given in full.

There is a generalized loss of phospholipids in the demyelinated areas in all conditions. The new cases of multiple sclerosis confirm previous findings not only as to the presence of cholesterol esters but

also as to the slight abnormality of the apparently normal areas. Changes in phosphoprotein phosphorus levels are discussed and suggestions for future investigations are outlined.

Neuraminic acid has been found to be raised not only in amaurotic family idiocy but also in all the demyelinating conditions so far examined.

It is suggested that it may be possible to assist diagnosis by the chemical examination of biopsy specimens of cerebral material and an example of such an examination is given.

I would desire to express my thanks to Drs. W. Blackwood, J. G. Greenfield and L. Phillips for autopsy material, and to Professor E. Klenk of Cologne for his gift to me of a sample of neuraminic acid. I also wish to express my indebtedness to Messrs. H. Goodwin and R. C. Shortman for their careful technical assistance. The cost of apparatus was defrayed by the Research Funds of the Institute of Neurology to whom I wish to express my thanks.

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MUSCLE SPINDLES AND OTHER SENSORY ENDINGS IN THE EXTRINSIC EYE MUSCLES; THE PHYSIOLOGY AND ANATOMY OF THESE RECEPTORS AND OF THEIR CONNEXIONS WITH THE BRAIN-STEM

BY

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THERE has been in the past much confusion over the nature of the proprioceptive supply of the extrinsic eye muscles and even over the existence of such an afferent system in these muscles. Failure to realize that receptor endings are in fact present in mammalian eye muscles, failure to take into account differences between species, failure to examine the whole length of human eye muscles, and the apparent absence of anatomically separate sensory roots to the third, fourth and sixth cranial nerves have led to doubts in some quarters about the existence of such a supply and in others to disagreement over its possible function. One school of thought, which has grown out of the views held by Helmholtz (1867), who wrote before there was any detailed conception of muscle sense, considers that a conscious knowledge of the voluntary effort which is needed to move the eyes, together with the messages received from the retina, makes any form of muscle sense unnecessary. Another school, impressed by the indispensability of muscle sense in the rest of the body musculature, and the positive evidence of the presence of sensory endings in the eye muscles, holds that these muscles depend on their own proprioceptors when they maintain or alter the posture of the globes to give that perfect adjustment which is essential to vision. Sherrington always held this view and expressed it most clearly in 1918.

The concept of muscle sense largely dates back to the early nineteenth century and the independent discovery by Bell and Magendie of the law of the spinal roots. As the science of histology developed, the microscopic structure of muscles became known and neuromuscular spindles were first recognized as anatomical units by Kölliker, in the

frog, in 1862, and Kühne, in mammals, in 1863; the latter author called the organ a "muskelspindel". Golgi in 1880 showed that there are nervous structures or tendon organs in the musculo-tendinous portions of mammalian muscles. After considerable discussion the function of these structures as proprioceptors was clearly established experimentally by Sherrington in 1894.

The electrophysiology of the muscle proprioceptors has been widely studied during the present century. The pioneer work of Adrian and Zotterman on the frog muscle spindle (1926) was followed by the work of Matthews (1933) in which the electrical discharges assumed to be from tendon organs and muscle spindle nerve endings in the hind-limb muscles of the cat were described. The discovery by Leksell (1945) that the group of small diameter motor nerve fibres going to a muscle serve as regulators of sensory activity originating in the muscle and probably activate the small intrafusal muscle fibres was another landmark. The recent work of Kuffler and Hunt (1952) has done much to elucidate muscle spindle activity in relation to this small-nerve or γ (gamma) efferent supply. A third of the motor nerve supply to a cat's limb muscle is concerned, not with producing tension, but with the activity of the muscle spindles. Sherrington (1894) showed that a third to a half of the fibres in a muscle nerve are sensory, thus as much as two-thirds of the whole nerve supply to a muscle is closely concerned with muscle sense and through it with the ultimate sensitivity of the motoneurones concerned with the production of tension in the muscle. The whole co-ordination of posture and movement begins to break down if the nerves subserving muscle sense are damaged.

Muscle spindles were looked for and found in most of the skeletal muscles of the body. Gregor (1904) gave figures for the numbers of muscle spindles in many muscles of a human fœtus. Sherrington was unable to find them in the extrinsic eye muscles of monkeys and cats (1894, p. 248), though he found many tendon endings in these muscles. Batten (1897), in an admittedly rapid survey, did not find muscle spindles in human eye muscles. The report of a muscle spindle in a human eye muscle by Buzzard in 1908 was hardly noticed except by Hughlings Jackson in one of his last papers with Paton (Hughlings Jackson and Paton, 1909). They write of the "out-going" and "in-coming" theories in relation to eye movement, with a strong bias towards the in-coming theory of messages from the eye muscles to the central nervous system. The work of Cilimbaris (1910) on the numerous muscle spindles in the extrinsic eye muscles of sheep was rarely quoted as proof of the presence of proprioceptors in mammalian eye muscles;

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whereas the negative evidence of the absence of spindles in the eye muscles of the common laboratory animals was much more widely known and was applied directly to human material.

Histological Studies of the Eye Muscles

Our own work on the extrinsic eye muscles began when one of us (Daniel, 1946) described spiral nerve endings, encircling some of the muscle fibres in the eye muscles of man. These spirals have a limited distribution in the muscle just distal to the very marked band of motor endings lying between the proximal and middle thirds of the muscle (fig. 1). A medullated nerve fibre is seen to encircle a single large dia-

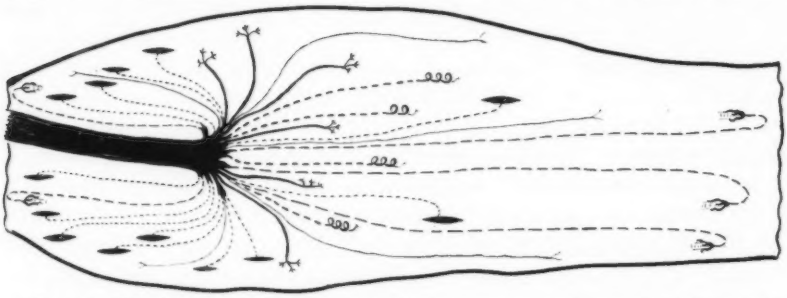

Fig. 1.—Much simplified diagram of a human rectus oculi muscle, full length. The origin of the muscle is on the left and the insertion on the right. The sensori-motor nerve (black trunk) is seen entering the muscle at the junction of the proximal and middle thirds. The muscle spindles are most numerous peripherally and in the proximal third of the muscle. Their nerves (composed of sensory fibres and gamma efferent fibres) are indicated by dotted lines. In the middle third of the muscle are the motor nerve endings whose nerve fibres are shown as solid black lines. Here also, mainly just distal to the band of motor nerve endings, are the simple spiral endings. At both the origin and insertion of the muscle tendon endings are seen (with their afferent nerve fibres shown as broken lines). The lines ending in small Ys represent nerve fibres supplying various of the other endings which are to be seen in eye muscles. (Compare this diagram with fig. 1 in Cooper and Daniel, 1949.)

meter muscle fibre three to eight times and then to end on that muscle fibre (figs. 23 and 25, Plate LV). The spirals are numerous, especially in the core of the muscle, and they must be affected by the thickening of the muscle fibres during contraction. It must be emphasized that the simple spiral endings do not form part of a muscle spindle. The double band of motor endings and simple spiral endings is so striking in any longitudinal section stained by the Bielschowsky-Gros silver method that it draws attention away from the rest of the muscle, which often does not stain so well.

It was only in the final stages of this work that a structure was seen, in transverse section in a region proximal to the motor endings in a human rectus oculi muscle, which resembled a muscle spindle. Two of us (Cooper and Daniel, 1949) then made a systematic search through all the human extrinsic eye muscles using a large variety of stains and taking care later to study muscles right back to the tendons of origin. The muscles, examined in transverse sections taken at about 4 mm. intervals throughout their length, are seen to have muscle fibres of differing diameter. From the belly to the tendon of origin there is a considerable peripheral layer of muscle fibres of small diameter, while close to both tendons almost all the muscle fibres are small. These small diameter muscle fibres are well supplied with nuclei, many of which are centrally placed. An occasional muscle fibre of very large diameter stands out among the small fibres. In the core of the muscle, especially in the belly, are muscle fibres considerably larger in diameter than those on the periphery (fig. 21*a* and *b*). These large muscle fibres are especially associated with the rich supply of motor nerve endings in the belly of the muscle and the simple spiral nerve endings just distal to the motor endings. The peripheral small muscle fibres undoubtedly remain of small diameter throughout their length, but we are uncertain whether the large diameter fibres in the core of the muscle stretch the whole length of the muscle and taper at their ends.

Transverse sections through the belly of a human eye muscle are found to be completely free from muscle spindles, and it is clear to us that in the past many investigators of eye muscles have confined their investigations of these muscles to a study of this region. When we examine the more proximal sections, muscle spindles are clearly seen in the peripheral layers of small diameter muscle fibres and among the small muscle fibres near the tendon of origin (figs. 22 and 24). The appearance of these muscle spindles agrees in the main with the classic description of these organs in limb muscles (Sherrington, 1894, pp. 240–244). There are 2 to 10 muscle fibres of small diameter enclosed in a capsule; an adjacent nerve trunk sends nerve fibres into this capsule which end on the intrafusal muscle fibres. The muscle spindles in the eye muscles (fig. 26, and *see* Cooper, Daniel and Whitteridge, 1954, fig. 184) differ in that the capsule itself is always a delicate structure, unlike the thick capsules often found in the spindles of the limb muscles. The muscle fibres often have central nuclei (fig. 27), but we never saw a large group or "bag" of clear nuclei in these intrafusal muscle fibres in human eye muscles, such as are found in the intrafusal fibres of limb

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muscles. In transverse sections a muscle fibre with a central nucleus is sometimes seen associated with a nerve ending (fig. 29).

On examining eye muscles in longitudinal sections, the arrangement of the muscle fibres of different diameters can be made out. The identification of muscle spindles is not easy owing to the delicate capsules (figs. 28 and 30) and the fact that the intra- and extrafusal muscle fibres are often of the same diameter. The search becomes a little easier in sections stained by silver methods. If the regions of the muscle outside the central band of motor and simple spiral nerve endings and their medullated nerve fibres have taken the impregnation well, many nerve fibres are seen among the peripheral layers of small diameter muscle fibres and near both the tendons of origin and insertion. Some of the tendon endings resemble Golgi tendon organs (1880); many other unusual types of ending are seen and are being further investigated. Our knowledge of the situation of the spindles in the muscle, gained from the study of transverse sections, was helpful in the search for muscle spindles. It is sometimes possible to detect a small nerve trunk going to a spindle-shaped collection of nerve fibres, nerve endings and intrafusal muscle fibres (fig. 28). If the spindle is not obscured by the nerve trunk, the outline of the capsule can occasionally be made out (fig. 30).

Delicate motor end plates on the intrafusal muscle fibres are seen at the poles of the spindles, and there is an elaborate arrangement of nerve fibres and endings at the equator. One at least of these latter nerve fibres is a thick medullated fibre which branches soon after entering the spindle. Other medullated fibres encircle all the intrafusal muscle fibres. The sensory endings are difficult to make out clearly, but they appear to be somewhat simpler than the endings found in the eye muscle spindles of the goat and sheep (Cooper, Daniel and Whitteridge, 1951) or in the limb muscle spindles of the cat and rabbit (Ruffini, 1898; Barker, 1948). It is worth remembering that the number and variety of endings in a spindle may vary even in the same species; in some of the muscle spindles described by Barker secondary endings were absent, as was the case in frog's muscle spindles described by Regaud and Favre (1904).

In each human extrinsic eye muscle there are about 50 muscle spindles, a comparable number with that found in a lumbrical muscle of the human hand. In the inferior rectus muscle about 45 of the muscle spindles were found to be situated near the origin of the muscle and the remaining 5 were scattered between the region of the simple spiral nerve endings and the tendon of insertion. A schematic plan of a human

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rectus oculi muscle is shown in fig. 1, which should be compared with fig. 1 in Cooper and Daniel (1949).

Merrillees, Sunderland and Hayhow (1950) confirmed the presence of muscle spindles in human eye muscles. They made counts on some of the muscles and found from 21 to 71 muscle spindles in an individual muscle.

We examined the extrinsic eye muscles of many animals and found that the higher apes have muscle spindles (fig. 20) and a still richer nerve supply to these muscles than that seen in man. In the extrinsic eye muscles of the artiodactyls, e.g. sheep and goats, we found that there are, as Cilimbaris had shown in 1910, many spindles (figs. 14, 15 and 17). These muscle spindles had "bags" of nuclei in the intrafusal muscle fibres; in good specimens of block impregnation these "bags" were clearly seen to be encircled by ribbon-like primary spiral nerve endings (figs. 18 and 19). Secondary spiral nerve endings could also be seen on these intrafusal muscle fibres (figs. 12, 13 and 16). In the lower monkeys, cats, dogs and many other animals no muscle spindles have ever been seen in the extrinsic eye muscles (Cilimbaris, 1910; Cooper and Daniel, 1949).

A further histological study was carried out on the extrinsic eye muscles of the monkey and cat (Cooper and Fillenz, 1955). In the monkey, an animal with a well-developed macula, the great size of the nerve trunks supplying each small extrinsic eye muscle is very striking. The innervation is particularly rich in both the proximal and distal tendons of each muscle and also in a considerable sheath of small diameter muscle fibres lying peripherally and covering a large part of the muscle. Many of these muscle fibres have central nuclei and so remind one of the intrafusal muscle fibres of muscle spindles, though they are not enclosed in any capsule. Some of these small diameter muscle fibres in the monkey's eye muscles have motor end plates at the end of a long fine nerve fibre; others are associated with a single nerve fibre that gives off a fine nerve ending at each node of Ranvier as may be seen in the cat (Cooper and Fillenz, 1955, Plate I, fig. 4); yet others have more complicated endings which clasp the muscle fibre. The wealth of endings throughout the muscle is such that it is difficult to enumerate and classify them all, though no muscle spindles were ever seen.

The cat's eye muscles have many of the histological features of the monkey's eye muscles, but to a lesser degree, for the nerve trunk is much smaller relative to the size of the muscle. The peripheral small diameter muscle fibres are present, but there are fewer of them. The

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nerve endings are many and varied and include occasional simple spiral endings.

Human eye muscles can perhaps be placed between those of the monkey and of the cat, as regards area of nerve trunk relative to muscle mass.

Electrophysiological Studies in the Orbit

The presence of muscle spindles in human extrinsic eye muscles encouraged us to see whether we could detect nerve impulses coming from the eye muscle proprioceptors and, since artiodactyls have so many muscle spindles in their eye muscles, we first worked on young goats and lambs (Cooper, Daniel and Whitteridge, 1951). We used the inferior oblique muscle, freed at its insertion and with its branch of the third nerve isolated and cut centrally. By cutting down a slip of the nerve till we had a single active nerve fibre we were able to record the impulses in this fibre using the standard cathode ray tube, amplifier and camera apparatus. Regular spontaneous units were detected and even a gentle stretch of the muscle would produce in one of these units a pattern of discharge (fig. 2) similar to that described by Matthews (1933) for the discharge of a muscle spindle nerve ending in a cat's limb muscle. The units in both cases have a low threshold for stretch, a high rate of discharge during the rising phase of the stretch, a slow rate of adaptation and a slowing or pause as the stretch is taken off; the rate of discharge varies with the degree of stretch and the duration of the rising phase. In the fibres of the third nerve afferent discharge rates of over 300 impulses/sec. have often been recorded. We were also able to record from an afferent fibre during a muscle twitch, which lasts about 15–20 msec. in a goat's eye muscle; the usual response here, with a just maximal stimulus, was a complete cessation of discharge during the brief rising phase of the twitch. This was followed by a burst of impulses during the relaxation period. This pattern of discharge is again characteristic of the discharge from a limb muscle spindle afferent ending in the cut peripheral nerve fibre during a maximal twitch. With a supramaximal stimulus we occasionally saw the unit discharging during the rising phase of the twitch, as Matthews (1933) described for his A_2 endings. This early response may have been caused by stimulating the γ efferent nerve fibres to the spindle.

Since each eye muscle in the goat contains a large number of well-developed muscle spindles (120 spindles were counted in the inferior oblique muscle of the goat by Cooper, Daniel and Whitteridge, 1951), it would have been surprising if we had failed to detect nerve impulses

travelling from the nerve endings in these organs to the brain-stem. Many other animals move their eyes voluntarily to a considerable extent, yet have no recognized low threshold stretch receptors, i.e. muscle spindles, in their eye muscles. Have they got such receptors in another form among the wealth of nerve endings present in their eye muscles? If typical low threshold receptor responses can be detected in nerve fibres coming from these muscles, then the answer is in the affirmative. A similar technique to that used on goats was used on cats (Cooper and Fillenz, 1955) and it was found possible to pick up single unit discharges in fibres of the branch of the third nerve from the inferior oblique muscle. The type of response (fig. 3), on stretching the muscle, was so similar to that from the primary nerve ending of a muscle spindle during stretch that we have no hesitation in ascribing it to a low threshold stretch receptor. Responses of this type were also recorded in fibres of the cat's fourth nerve on stretching the superior oblique muscle (fig. 4). A similar response was obtained from the inferior oblique nerve of one monkey. Both cat and monkey showed a second type of long latency, quickly adapting response to a sharp stretch. This we took to be from another variety of ending.

From experience with these three types of animal we think it highly probable that all mammals with voluntary eye movements have low threshold stretch receptors in their eye muscles. Thus, as a result of this electrophysiological work on animals it would appear that man has such receptors; in confirmation the histological evidence from human eye muscles shows us muscle spindles which we know to be sensory, and other endings, such as the simple spirals, that we take to be sensory.

The Pathway to the Brain-Stem

So far we have established that proprioceptive impulses are set up in the extrinsic eye muscles, but there is no clear-cut and obvious pathway for these impulses to take on their way to the brain. Since obvious anatomically separate sensory roots on the third, fourth and sixth cranial nerves are absent, there appear to be two alternatives: either the so-called motor roots carry the sensory impulses, or such impulses go by the fifth cranial nerve. There are many old observations that in man the eye muscle nerves send small branches to the ophthalmic division of the fifth nerve in the cavernous sinus. Extensive dissections were done by Stibbe; he gives a short account of them in 1929 and they are illustrated in Whitnall's book on the human orbit (1932, p. 334). Unfortunately the fuller description of Stibbe's work was only printed

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privately and never published. In this latter work he also gives histological proof of connexions.

Extensive dissections of the nerves of many mammalian orbits were carried out by Winckler (1932); he sometimes noticed anastomoses between the fifth nerve and the eye muscle nerves, and in the goat he saw small nerves leaving a branch of the fifth nerve to enter the superior oblique muscle. Kiss (1935) carried out similar dissections and, in particular, he illustrates extensive connexions between the fifth nerve and the eye muscles in the antelope. Winckler published further studies in 1936 on the pig, and in 1937 on the sheep, goat and cow. He showed clearly that the recti oculi muscles each have a double nerve supply, the recognized motor supply and a branch, or often branches, going to the fifth nerve. These branches usually leave the muscle on the opposite face to the entry of the main motor nerve. Some small branches from the superior oblique muscle pass directly to the fifth nerve in the orbit, while the fourth nerve itself always sends a branch to the fifth nerve near the cavernous sinus. The branch from the inferior oblique muscle travels with the third nerve to the ciliary ganglion and then joins the fifth nerve. Winckler suggests that all these branches from the eye muscles to the fifth nerve carry proprioceptive impulses from the eye muscles.

The presence of these branches has been fully confirmed by us in the goat, and by leading from them, using the superior oblique muscle, Whitteridge (1955) has shown that they do indeed carry proprioceptive impulses (fig. 5). It was again possible to record typical low threshold responses to stretch that we now associate with the primary nerve endings of the muscle spindles in the goat's eye muscles. This important confirmation of a separate sensory pathway made it possible to investigate our problem further, since a muscle with a pure sensory nerve was now being used. It was possible to record from sensory fibres from the superior oblique muscle before and after cutting the fourth nerve. The sensory discharge when the motor nerve was intact showed certain irregularities which disappeared when the motor nerve was cut. The irregularities are probably due to the presence of intact γ efferent nerve fibres to the muscle spindles (Eldred, Granit and Merton, 1953).

The presence of separate sensory pathways from some of the eye muscle proprioceptors to the fifth nerve in one group of animals, and the probable presence of proprioceptors in all mammalian eye muscles makes it very likely that similar pathways exist outside the artiodactyl group. A search in man, baboon and cat, using the binocular microscope, has convinced us that nerve branches certainly run from the

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fourth to the fifth nerve, but the site of the connexion is extremely variable and it is usually to be found right at the back of the orbit in the superior orbital fissure, or in the cavernous sinus. In man the presence of small branches from the third and sixth nerves to the fifth nerve was confirmed.

In the decerebrate cat, after cutting the frontal nerve in the orbit an attempt was made to find a connexion between the fourth and fifth nerves and to lead off from each nerve central to this connexion (Cooper, unpublished observation). Bleeding in the cavernous sinus often made this difficult, but in one cat stretching the superior oblique muscle gave a low threshold sustained response in the fifth nerve and a long latency quickly adapting response in the fourth nerve. Two types of receptor may thus be sending their messages into the brain by different pathways. In other cats very small nerves have been seen to leave the fourth nerve close to the superior oblique muscle and to make their way, within the orbit, to the fifth nerve. These small nerves carried slowly adapting nerve impulses in response to stretching the superior oblique muscles. Typical quickly adapting touch or pain discharges were never seen in these nerve fibres from the superior oblique muscle; hence we were not leading from fibres which leave the muscle again peripherally, as described by Wilkinson (1930).

Thus there are indeed connexions between the eye muscles and the fifth nerve in most animals. These branches probably vary considerably in size in different animals according to the number of low threshold stretch receptors which are present in the eye muscles in the different species. On re-reading Tozer and Sherrington (1910) we are struck by the careful record of a few degenerating nerve fibres going to the eye muscles after section of the ophthalmic division of the fifth nerve in monkeys. Degenerating endings were not seen in the muscles by these authors; but such endings might easily be missed in the extraordinarily rich innervation found in these muscles, unless a complete set of well-stained serial sections was examined. The emphasis in this paper was on the insertion end of the muscle and the authors may not have studied in detail the origin end, which is just as richly supplied by nerves and which, as we have shown in human material, is particularly associated with muscle spindles.

Electrophysiological Studies in the Brain-Stem

We have proved so far on histological grounds that proprioceptors exist in the extrinsic eye muscles of certain species, including man. By extending the work, using electrophysiological methods, we have shown

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that the nerves from the eye muscles carry proprioceptive impulses from stretch receptors. This we find to be true whether or not the eye muscles contain organized stretch receptors of a known type, e.g. muscle spindles. Some of these impulses may reach the brain-stem in the eye muscle nerves; so far as we can judge, it is the high threshold receptors, which may include the tendon receptors, that send their messages in this way; they may have their cells of origin in the eye muscle nuclei or in the scattered cells and small ganglia known to lie along the third and sixth nerves. The low threshold receptors, i.e. the primary nerve endings of muscle spindles, where the latter exist, or the analogous endings in the other cases, send their impulses, we believe, in fibres which finally join the ophthalmic division of the fifth nerve; and we have confirmation of this on anatomical grounds. To complete this evidence we decided to look for the cells of origin of these sensory neurones and to trace the final pathways into the brain-stem.

We have already suggested (Cooper, Daniel and Whitteridge, 1953*a*) that the cells of origin of the low threshold sensory receptors may lie in the Gasserian ganglion, or inside the brain-stem in the mesencephalic nucleus of the fifth nerve. The latter nucleus is known to contain the sensory cells for the jaw muscle proprioceptors (Corbin and Harrison, 1940), but the increase in the number of its cells near the nuclei of the third and fourth cranial nerves has often aroused the suspicion that the proprioceptors of the eye muscles may have cells of origin here.

We decided to use a steel micro-electrode for detecting impulses within the brain-stem in response to stretch of the goat's eye muscles (Cooper, Daniel and Whitteridge, 1953*a*, *b* and *c*). The animals were usually anæsthetized with sodium pentobarbitone (Nembutal), or sometimes they were decerebrated. A few mangabey monkeys and a baboon (*Papio papio*), under sodium pentobarbitone, were also used later. The position of the needle tip was directed by the use of a stereotaxic machine; the impulses were recorded with the cathode ray tube, amplifier and camera apparatus. The position of the needle was confirmed after each experiment by extensive histological work. Our results had to be compiled from a large number of experiments, owing to the technical problems of any one experiment. We tried to have the anæsthetized animals under comparable conditions; this is less important for work on the first neurone, but for studying the behaviour of second or later neurones it becomes essential, since the effects of anæsthetics on synaptic transmission are imperfectly understood, though undoubtedly they have a great influence. Two other precautions had to be taken: one was to guard against the possible influence of pain and other impulses from

periorbital tissues, the other was to be sure that the jaw muscles had no direct mechanical influence on the eye muscles, and *vice versa*, in an animal with an open bony orbit. This latter precaution was, of course, not necessary in the monkeys or baboon with their complete bony orbits.

We had no difficulty in confirming the finding of Corbin and Harrison that the majority of cells of the mesencephalic nucleus of the fifth nerve give rise to the proprioceptors of the jaw muscles. We obtained a number of records of single units which arose from muscle spindles in the jaw muscles (Cooper, Daniel and Whitteridge, 1953*a*, text-fig. 3).

Our search to find the central path of the first neurone from an eye muscle receptor did not prove to be easy, though we gained much other information about later pathways taken by the discharges. In only two regions can we state with conviction that we detected first neurone responses. One site was a large cell similar in type to, and probably part of, the mesencephalic nucleus of the fifth nerve. It was situated near the midline of the dorsal aspect of the central grey matter just ventral to the posterior commissure. The other sites were all among the fibres of the fifth nerve as they passed through the pons. In both regions the discharges (figs. 6*a* and 7) were in response to stretch of a single eye muscle, individual units were brought in or accelerated, the latency was short, the impulses reached a high rate of discharge, especially during the application of the stretch; they were slowly adapting and stopped abruptly as the stretch was taken off, and there was often a pause before the resting rate was resumed. Fig. 6*a* and *b* makes clear the similarity of the peripheral and the brain-stem responses to stretch of an eye muscle. There are some slight irregularities in the brain-stem response which again may well be due to the activity of the intrafusal muscle fibres of the muscle spindles with an intact γ efferent supply influencing in a small degree the responses of the primary sensory ending (Eldred, Granit and Merton, 1953).

Further confirmation of these results has been obtained in the cat (Fillenz, 1955), where responses to stretching the eye muscles have been picked up from cells of the mesencephalic nucleus of the fifth nerve.

Though some of the cells of origin of the eye muscle low threshold stretch receptors lie in the mesencephalic nucleus of the fifth nerve, it is still a matter for speculation how the sensory fibres pass from the ophthalmic division of the fifth nerve to this nucleus. The motor root of the fifth nerve is the accepted pathway for sensory impulses from the muscle spindles of the jaw muscles to the nucleus. In man we have

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several times seen small branches passing between the ophthalmic division and the motor root of the fifth nerve on the central side of the Gasserian ganglion. These branches would provide a possible pathway for the impulses from the low threshold stretch receptors of the eye muscles.

After leaving the first neurone and entering later pathways, the pattern of the responses in the brain-stem to stretch of the eye muscles begins to change, and the latencies of the responses to lengthen. We were particularly interested in the single unit responses picked up in the central tegmental group of tracts and the immediately adjacent regions, since their pattern often suggested that of a distorted first neurone response from a low threshold stretch receptor (figs. 8, 9 and 10). Responses from limb proprioceptors were also detected in these tracts which pass close to the motor nuclei of many of the cranial nerves. Other responses to stretching the eye muscles were picked up in the medial longitudinal fasciculus, in or near the fibres of the eye muscle nerves and in cerebellar pathways; these single unit responses had long latencies and the pattern was unlike that of the low threshold stretch receptor responses. Other multi-unit responses were heard in the eye muscle nuclei themselves and in the deeper layers of the superior colliculus. Later work on the cat and baboon has also shown that responses to stretching the eye muscles can be detected in the medulla oblongata (fig. 11). The finding of impulses in many of these sites suggests the presence of connexions between the eye muscle proprioceptor neurones and other centres which are known to be closely linked with eye movements. The responses in the superior colliculus suggest a close connexion between the eye muscles and the retina, since sharply localized responses, often consisting of single units, can be detected in the colliculus to localized stimulation of the retina with light flashes (Cooper, Daniel and Whitteridge, 1953*c*). This confirms the work of Apter (1945) on the cat. Further work on the optic tectum of the pigeon has been carried out by Hamdi and Whitteridge (1954) and work on the superior colliculus of the rabbit is in progress. We have some evidence that the close association of eye muscle receptor responses and visual responses also occurs in the superior colliculus in the monkey. A similar association probably takes place in man and helps to bring about the optimum positioning of the foveæ to view an object.

The inability to record a stretch reflex in the eye muscles has in the past been one of the arguments used against the presence of stretch receptors in these muscles. But it must not be forgotten that most of the work on stretch reflexes has been carried out on the extensor muscles of

the limbs and on the anti-gravity muscles of the jaw. The animal experiments are usually carried out against a background of extensor rigidity or with special techniques to condition the motoneurones. The flexor muscles of the limbs are as well, if not better, endowed with those proprioceptors that are claimed to be the stretch receptors, i.e. the muscle spindles, as the extensors, yet a sharp pull on the flexor muscles can at most give a brief pluck reflex and not the maintained stretch reflex as seen in the extensors. The result of stretching a flexor muscle is best demonstrated by showing its inhibitory effect on the tone of its antagonist, or, in the decerebrate animal, on the stretch reflex of the antagonist (Liddell and Sherrington, 1925). The eye muscles are specialized muscles, and they cannot be classified either as flexors or extensors. McCouch and Adler (1932) were unable to record a stretch reflex in the eye muscles of the cat. We were usually unable to get such a reflex in the eye muscles of the goat, but in occasional animals with marked decerebrate rigidity we can perhaps say that our results were inconclusive.

Discussion

Our aim in this work was to confirm the presence of proprioceptors in the extrinsic eye muscles and to trace the pathway for the impulses from such receptors into the brain-stem. In man, the higher apes, and the artiodactyls some of these receptors take the form of muscle spindles whose primary nerve endings act as low threshold stretch receptors. It is interesting that these encapsulated organs are not present in the extrinsic eye muscles of all species of animals, though electrophysiological work has shown us that some other neuromuscular structure is capable of acting as a low threshold stretch receptor. A great deal of new light has been thrown recently on the discharges of stretch receptors in the limb muscles by the work of Kuffler and Hunt (1952), Granit (1955), and others. It is becoming increasingly clear to us that in many respects we can compare the activities of the eye muscle proprioceptors with those in the limb muscles, though there is much more to be learned in both cases.

To throw some light on the differences between the eye muscles in different species and between the eye muscles and the limb muscles we must look to the structure of the muscles themselves. The mammalian limb muscles have reached a fairly stabilized state in their evolution. Many of the cranial muscles have developed differently, probably to meet the particular needs of each group of animals, so that the morphology of the muscle fibres and their nerve endings may differ in different

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species, though basically their activities may vary only in degree. These species differences are well seen in the eye muscles, and also in the intrinsic muscles of the tongue supplied by the twelfth nerve (Cooper, 1953, 1954). A further study of the nerve endings in the muscles supplied by the seventh and ninth nerves might also prove interesting.

The eye muscles of many mammals show a very striking layer of small diameter muscle fibres, often with central nuclei, forming the peripheral part of each muscle. The fact that muscle spindles, when present, nearly always lie close to or among these small diameter muscle fibres suggests some affinity between the extra- and intrafusal muscle fibres of this region which are often of very similar diameter. In those animals without muscle spindles in their eye muscles, the muscle fibres associated with the low threshold stretch receptors probably lie among the small diameter, richly innervated muscle fibres in the periphery of the muscle (Cooper and Fillenz, 1955).

These small diameter muscle fibres of the periphery of the eye muscles may have a closer affinity with the intrafusal fibres of mammalian limb muscle spindles than we yet perfectly understand. Many of the muscle fibres of the eye muscles and the intrafusal muscle fibres of the limb muscles appear to be somewhat immature in form. Certain drugs which act on eye muscles, e.g. acetylcholine, which causes a prolonged contraction (Duke-Elder and Duke-Elder, 1930; Brown and Harvey, 1941), and curare, with its early paralysing action, call to mind the pharmacological work of Hunt (1952) and Granit, Skoglund and Thesleff (1953), who described the effects of drugs on the intrafusal muscle fibres of limb muscle spindles. More such work on mammalian intrafusal muscle fibres, on embryological muscles, and on submammalian forms of muscle may throw interesting light on the activities of the eye muscles.

We can as a result of our present knowledge say that human extrinsic eye muscles are richly endowed with a degree of sensibility that bears comparison with that in those limb muscles with the greatest sensory innervation (e.g. the lumbricals of the human hand). In addition, we have proof that in those eye muscles that contain muscle spindles there is a γ efferent nerve supply to the intrafusal muscle fibres of the spindles. These organs thus have their own reflex loop which is likely to play a large part in the segmental activities of the muscles. The γ motoneurones are probably under the influence of the retinæ and the periorbital tissues in much the same way that the γ efferents to the intrafusal muscle fibres of the muscle spindles of the extensor muscles of the limbs are affected by the skin and joints. The extrinsic eye muscles also have

close connexions with the cerebellum and the brain-stem, so that those influences, termed by Granit "supraspinal" when he is dealing with the limb muscle receptors, must also be of importance in controlling the discharges in both the α and γ efferent nerve fibres.

If we wish to endow the eye muscle proprioceptors with a direct and conscious effect in visual experience, we are on difficult ground. There is very little reliable evidence that messages from the limb muscles reach consciousness; but we do know, firstly, that many complex muscular actions can take place without the cortex, provided the muscle proprioceptors are intact, and, secondly, that the cortical superstructure may fail in its efforts for muscular control if the sensory side of the lower reflex arcs is inactivated, as may well be seen in tabes dorsalis.

In relation to the control of ocular movement, Gordon Holmes, writing in 1921, speaks of *"the complex physiological apparatus which regulates the normal movements of the eyes. For these occur not only in response to voluntary impulses, but also as reflex movements excited by peripheral stimuli arising in the retinæ, in the ocular muscles themselves, in the labyrinths, in the cervical muscles, and even in response to auditory and cutaneous stimuli. Further, while some of these reflex movements, such as the adjustments of our eyes to changes in the position of our heads and bodies, depend on the activity of sub-cortical centres only, others require the intervention of the forebrain cortex."* We have been concerned in this paper only with those stimuli "arising in the ocular muscles themselves" and are convinced that every eye movement, whether it be voluntary or reflex, tiny as in saccadic fixation movements or large as in some forms of nystagmus, is recorded accurately and indefatigably in the brain-stem by the eye muscles. Such a recording must play an important part in maintaining or attempting to maintain the eyeballs in the optimum position for vision and in keeping them in readiness to be moved at will.

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LEGENDS FOR PLATES

PLATE LI

FIG. 2.—Goat. Response to stretching the inferior oblique muscle showing afferent discharges of a muscle spindle recorded from the third nerve. Above; time 1/10 sec. : stretch signal.

FIG. 3.—Cat. Response to stretching the inferior oblique muscle, showing afferent discharges of an ending in the muscle, recorded from the third nerve. Below; time 50 c/s : stretch signal.

FIG. 4.—Cat. Response to stretching the superior oblique muscle, showing afferent discharges of an ending in the muscle, recorded from a small branch leaving the muscle near the fourth nerve (spikes retouched). Above; time 50 c/s : below; stretch signal.

FIG. 5.—Goat. Response to stretching the superior oblique muscle. The afferent discharges from a muscle spindle were recorded in a sensory nerve passing from this muscle to a branch of the fifth nerve. Below; time 50 c/s : stretch signal.

PLATE LII

FIG. 6.—Goat, under Nembutal anæsthesia. *a*, Central responses to stretching the superior oblique muscle recorded from a large cell of the mesencephalic nucleus of the fifth nerve, ventral to the posterior commissure (the gap in the record indicates a time of 6/10 sec.). Below; time 50 c/s : stretch signal. *b*, Another goat. Peripheral response to stretching the inferior oblique muscle, for comparison with the central response in *a*. The afferent discharges from a muscle spindle were recorded in the third nerve. Above; time 1/10 and 1/100 sec. : stretch signal. Note the remarkable similarity of the responses in the brain-stem and in the peripheral nerve. The former are slightly irregular, probably owing to the activity of intact γ efferents.

FIG. 7.—Goat. Decerebrate. Central response to stretch of the superior oblique muscle recorded from fibres of the fifth nerve within the brain-stem. Below; time 50 c/s : stretch signal.

PLATE LIII

FIG. 8.—Goat. Decerebrate. Slightly delayed central response to stretch of the superior oblique muscle recorded from the brain-stem close to the motor nucleus of the fifth nerve. Above; time 50 c/s : below; stretch signal.

FIG. 9.—Goat, under Nembutal anæsthesia. Delayed central response to stretch of the medial rectus muscle recorded from the region of the central tegmental tract, ventral to the inferior colliculus. Above; time 50 c/s : below; stretch signal.

FIG. 10.—Mangabey monkey, under Nembutal anæsthesia. Delayed central response to stretch of the inferior oblique muscle recorded from the region of the central tegmental tract ventral to the motor nucleus of the fifth nerve. Above; time 50 c/s : below; stretch signal.

FIG. 11.—Baboon (*Papio papio*), under Nembutal anæsthesia. Central response to stretch of the inferior rectus muscle recorded from the medulla oblongata just dorsal to the rostral end of the respiratory centre. Above; time 50 c/s : below; stretch signal. There is a signal artefact at start of stretch.

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PLATE LIV

FIG. 12.—Sheep. Longitudinal section of a superior oblique muscle showing intrafusal muscle fibres lying in the periaxial space of a muscle spindle. Two of the muscle fibres have fine spiral secondary endings, each of which takes many turns around the muscle fibre. *a* and *b* show the same structures at two different depths of focus. (Cajal block silver impregnation.)

FIG. 13.—Sheep. Longitudinal section of a rectus oculi muscle showing part of the spiral secondary ending on an intrafusal muscle fibre of a muscle spindle. In *a* and *b* the same ending is shown at two different depths of focus. (Cajal block silver impregnation.)

FIG. 14.—Young sheep. Longitudinal section of a rectus oculi muscle to show a muscle spindle. Note the intrafusal muscle fibres and the large periaxial space. (Hæmatoxylin and van Gieson.)

FIG. 15.—Sheep. Transverse section through a muscle spindle in a rectus oculi muscle. Note the well-defined capsule, the nuclei in which suggest that there is an encircling nerve fibre. Each of the seven intrafusal muscle fibres, in the lower group, contains a central nucleus. There is also an intrafusal muscle fibre with peripheral nuclei, and, above it, a blood vessel. The large periaxial space is crossed by wisps of connective tissue. (Hæmatoxylin and eosin.)

FIG. 16.—Sheep. Longitudinal section of a superior oblique muscle showing part of a muscle spindle with its fine capsule. Nerve fibres are seen approaching the intrafusal muscle fibres from the right, and there are complex spiral nerve endings on all these intrafusal muscle fibres. Part of an extrafusal muscle fibre is seen on the left. (Cajal block silver impregnation.)

FIG. 17.—Young sheep. Transverse section of a rectus oculi muscle showing two muscle spindles. Note the central nuclei in the intrafusal muscle fibres and the large periaxial spaces. (Hæmatoxylin and van Gieson.)

FIG. 18.—Goat. Longitudinal section through the equatorial region of a muscle spindle in a rectus oculi muscle. The section is through the "bag" of nuclei in an intrafusal muscle fibre and shows the spiral, ribbon-like primary nerve ending either cut across or as rather granular strips. (Cajal block silver impregnation.)

FIG. 19.—Sheep. Longitudinal section of a rectus oculi muscle showing the equatorial region of the intrafusal muscle fibres of a muscle spindle. One "bag" of nuclei is in focus with its spiral nerve ending cut across in several places. (Cajal block silver impregnation.)

PLATE LV

FIG. 20.—Chimpanzee. Transverse section of a muscle spindle in a rectus oculi muscle. Note the clearly defined capsule and the small diameter of the intrafusal muscle fibres, one of which has a central nucleus. (Hæmatoxylin and eosin.)

FIG. 21.—Human lateral rectus muscle. Transverse sections showing different diameters of muscle fibres. *a*, large diameter fibres lying in the core of the muscle. *b*, small diameter fibres lying around the periphery of the same muscle. (Hæmatoxylin and eosin.)

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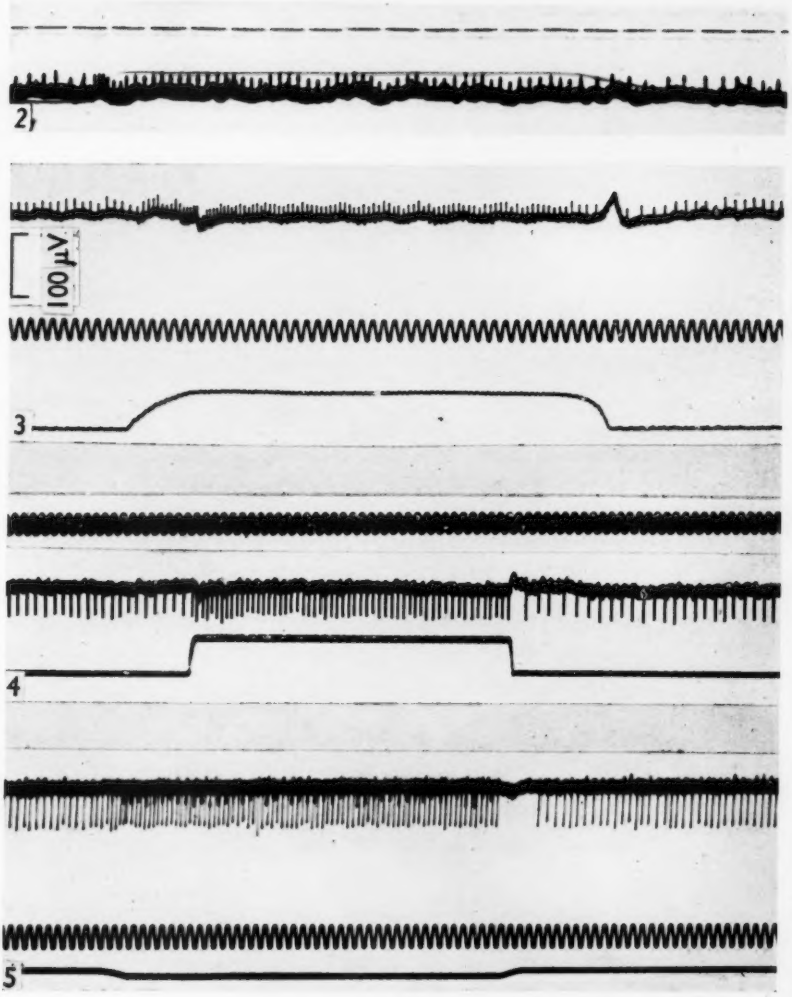

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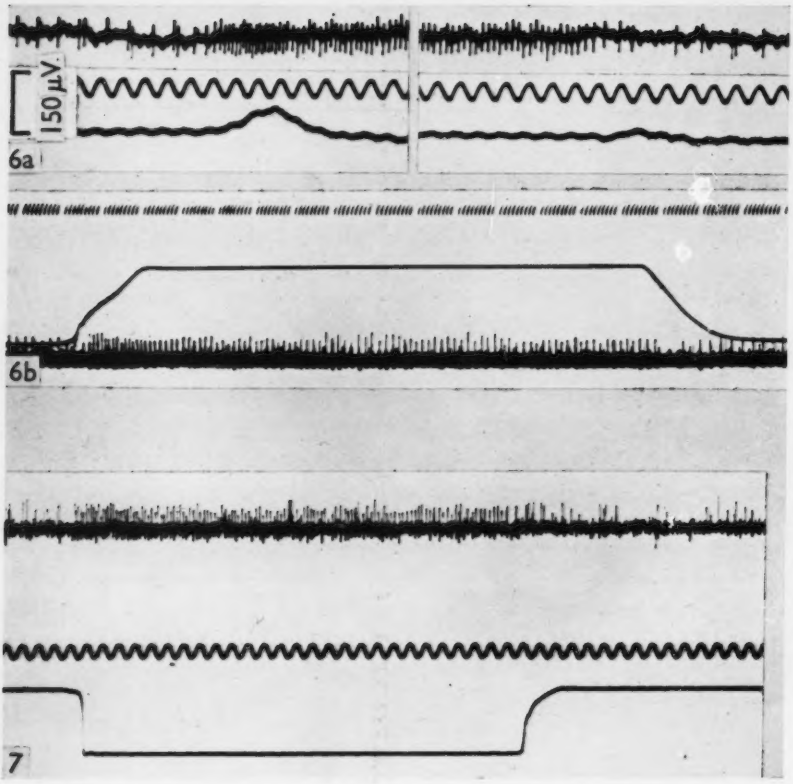
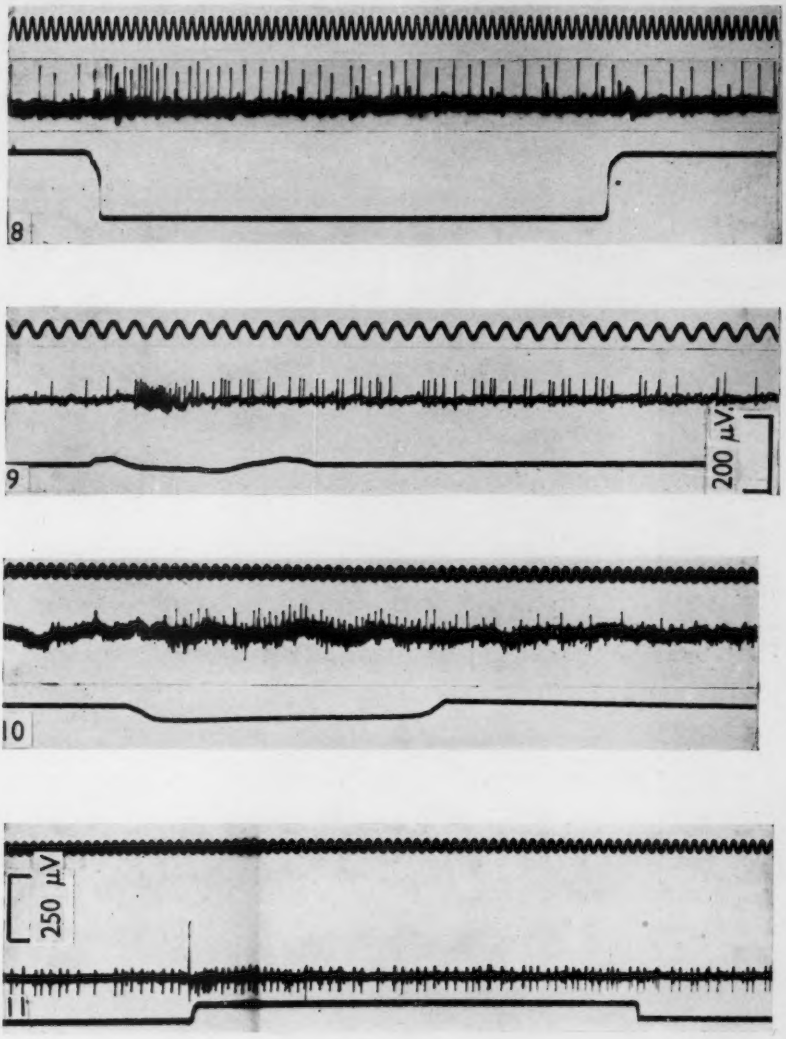
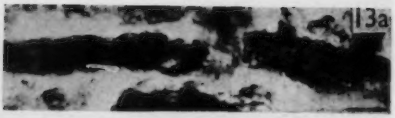


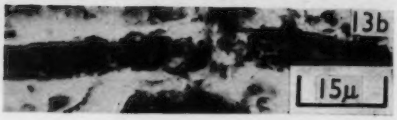
To illustrate article by Sybil Cooper, P. M. Daniel and D. Whitteridge.

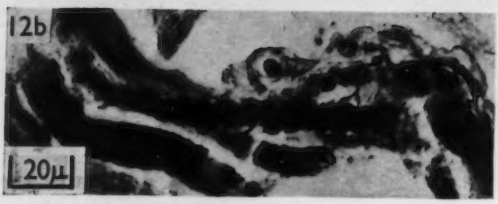
PLATE LIII

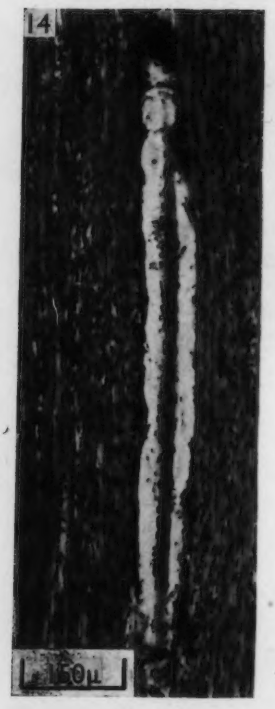


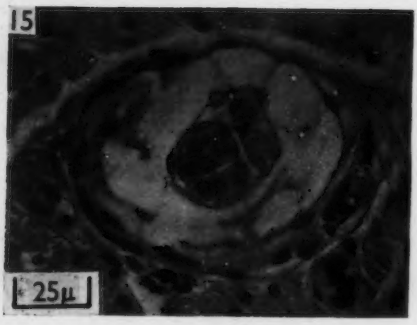
To illustrate article by Sybil Cooper, P. M. Daniel and D. Whitteridge.











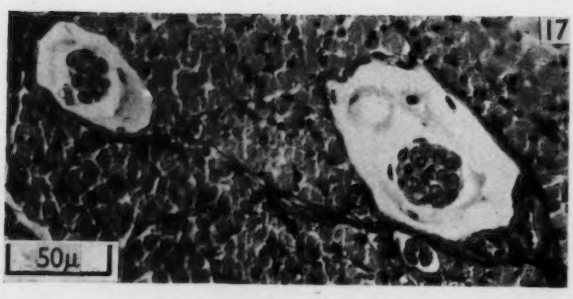


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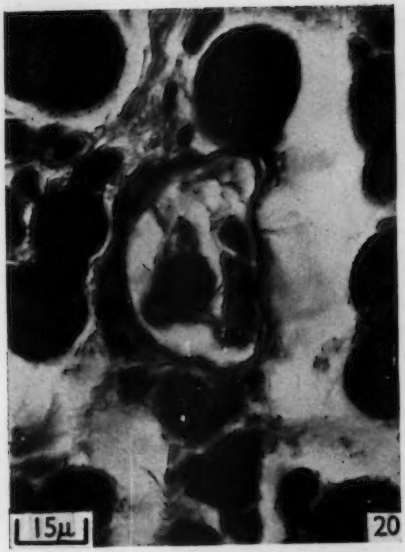
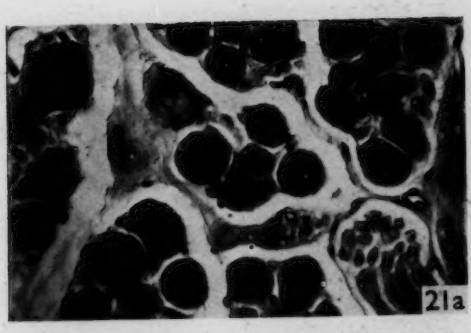
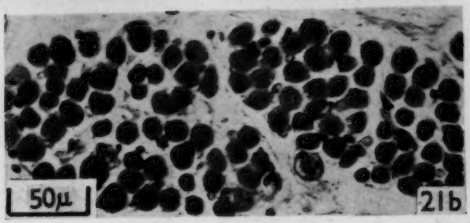
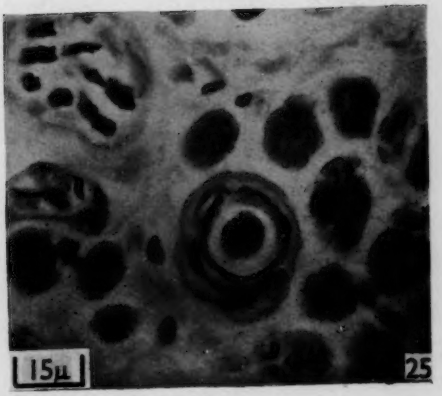
PLATE LV









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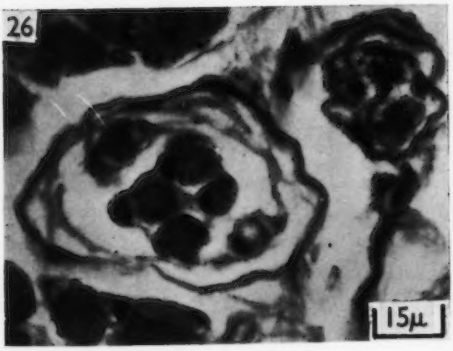

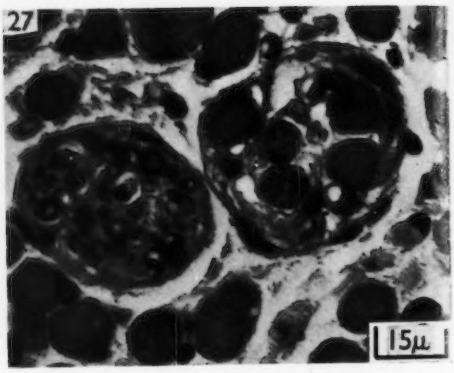

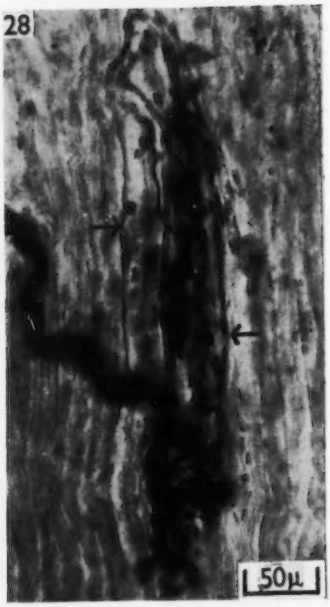

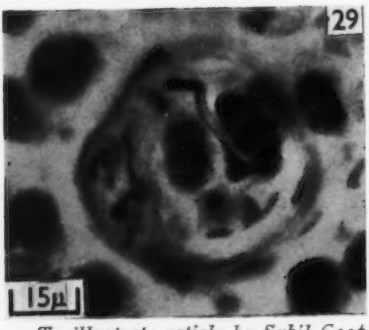

To illustrate article by Sybil Cooper, P. M. Daniel and D. Whitteridge.

FIG. 22.—Human rectus oculi muscle. Transverse section showing a muscle spindle and adjacent nerve trunk (upper right). (Hæmatoxylin and van Gieson.)

FIG. 23.—Human lateral rectus muscle. Transverse section showing simple spiral nerve fibre around an extrafusal muscle fibre. (Holmes' silver method.)

FIG. 24.—Human medial rectus muscle. Transverse section showing a muscle spindle. Note that the intrafusal muscle fibres are of approximately the same diameter as the extrafusal fibres. There is much connective tissue within the main capsule of the spindle. The upper right intrafusal muscle fibre has a central nucleus. (Hæmatoxylin and eosin.)

FIG. 25.—Human medial rectus muscle. Transverse section showing simple spiral nerve fibre encircling an extrafusal muscle fibre. The outline of the sheath of Schwann around the nerve fibre can be seen. (Holmes' silver method.)

PLATE LVI

FIG. 26.—Human rectus oculi muscle. Transverse section showing a muscle spindle and adjacent nerve trunk (upper right). Note that the capsule of the spindle is extremely delicate. In this specimen there has been considerable shrinkage of the tissue. (Hæmatoxylin and van Gieson.)

FIG. 27.—Human rectus oculi muscle. Transverse section showing a muscle spindle adjacent to a fairly large nerve trunk (left). There has been little shrinkage in this specimen so that the capsule of the spindle is less obvious and there is a considerable quantity of intra-capsular connective tissue. Note the central nucleus of one of the intrafusal muscle fibres. (Hæmatoxylin and eosin.)

FIG. 28.—Human. Longitudinal section of a lateral rectus muscle of a child. Part of a muscle spindle is seen. Note the delicate capsule (arrows). A nerve trunk approaches the spindle from the left and nerve fibres can be seen entering the spindle and also inside the capsule. (Thick frozen section. Bielschowsky-Gros silver method.)

FIG. 29.—Human. Transverse section of a lateral rectus muscle showing a nerve ending on an intrafusal muscle fibre. A small nerve trunk is seen in the wall of the capsule (on the left). (Holmes' silver method.)

FIG. 30.—Human. Longitudinal sections of an inferior rectus muscle showing a muscle spindle. Numbers of intrafusal nerve fibres are seen. In *a* the nerve trunk supplying the spindle can be seen (bottom right). Note also in *a* the cross striations of an intrafusal muscle fibre (arrow). The capsule of this spindle is very delicate and tenuous. *a* and *b* are adjacent sections from a serial set. (Holmes' silver method, counterstained, with light green.)

CUTANEOUS SENSATION AND THE DOCTRINE OF SPECIFIC ENERGY

BY

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INTRODUCTION

MANY sensations may be elicited by stimulating the normal skin, and many others by stimulating skin in which the sensory innervation has been damaged. These sensations can be roughly classified according to their introspective relationships, and it is accepted that there are four main taxonomical groups—touch, pain, cold and warm—though the exact classification of a given sensation may be difficult. In some experimental and pathological situations the sensations grouped under a given heading appear to behave differently from those grouped under another, and the generally accepted explanation of their mutual independence is that they are mediated by anatomically separate neural mechanisms. This theory is standard doctrine in most medical textbooks, but recent work on the anatomy and physiology of cutaneous sensation has made it desirable to reopen the question. It is perhaps helpful to begin with a brief account of the way in which our beliefs have developed.

The doctrine of specific energy.—It was Johannes Müller (1838) who first clearly formulated the idea of an intrinsic difference between the nervous mechanisms subserving the five senses, so that the same stimulus could produce two different sensations if applied to two different kinds of nerve. Müller expressed his concept in the term "specific energy," which implies a qualitative distinction between the five kinds of nerve. Nevertheless he gave this specificity an anatomical habitation by maintaining that it lay in the central portion of the nerve or in its termination in the brain rather than in the periphery. Conversely, he believed that the peripheral terminations of nerves were in some way specialized to react preferentially to certain stimuli—a principle which he termed "specific irritability." He did not claim any specificity extending along the whole length of the nerve fibre.

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Müller's ideas were quickly extended to apply to individual sensations. Thus Volkmann (1844) suggested that within the compass of the nerves allotted to cutaneous sensation there must be separate nerves mediating pressure, temperature and tickle. This concept was later supported by the discovery in the skin of a mosaic of tiny "spots," each reacting preferentially to its own particular type of stimulus (Blix, 1884). Meanwhile histological investigation had disclosed the presence of different types of nerve-ending in the skin, and von Frey (1894, 1895, 1896) put flesh on the bones of Müller's "specific irritability" by suggesting that in relation to each sensory spot there lay a morphologically distinct end-organ or group of end-organs. From von Frey's papers also dates our belief in the specificity of the whole length of the sensory neuron subserving a given sensation.

Müller's suggestion that the "specific energies" of the five senses have as their destination circumscribed anatomical areas in the brain has since been abundantly confirmed. However, this idea has not yet been extended to include specific topographical representation of individual cutaneous sensations within the territory allotted to cutaneous sensation. In spite of this, as a result of observations initiated by Brown-Séquard (1863) on lesions of the spinal cord, we have come to believe that introspectively distinct cutaneous sensations are mediated within the central nervous system by anatomically distinct pathways.

Both Müller and von Frey were essentially theoretical; Brown-Séquard was more practical. It was the further development of the practical approach which led to the first (and only) major heresy within the doctrine of specific energies. After observing the progress of a deliberately inflicted nerve lesion, Head (1920) advanced the idea of two functionally distinct systems of cutaneous nerves, one being specialized to subserve coarse impressions resulting from moderate or intense stimulation, and the other to convey the finer gradations of cutaneous sensation. These two kinds of nerve fibres were thus not "specific" in the way that the Müller-Volkmann-von Frey fibres were, though Head's sensory system still contained two sets of fibres which were anatomically separate and functionally distinct. The idea attracted many people, and for a time the orthodox position was seriously threatened. However, all but a few of Head's experimental results could be explained without recourse to his theory, and it subsequently transpired that these crucial findings could not be duplicated by other observers.

The doctrine of patterns.—In recent years there has been a revulsion from the comfortingly rigid Victorian idea of the nervous system as a telephone exchange, and this has found one expression in the suggestion

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that a specific cutaneous sensation results when the brain receives from the skin impulses which make up a characteristic pattern. Thus Nafe (1927, 1929), using as a basis the electrophysiological work of Adrian and Zotterman, suggests: "Regardless of the number and amount of its complications the neural excitation remains a temporal and spatial arrangement or pattern of a number of impulses and as such may be accompanied by a related conscious experience. In all these complications of 'patterns of discharges' there are no new elements. Familiar patterns are named, and, if an experience arises for which we haven't names enough, we supplement our descriptions with qualifying adjectives . . ." Nafe "restates" Müller's hypothesis as follows: "The specific accompaniment of sensory excitation is correlated with the number of nervous impulses and their temporal and spatial relations." Clearly this is no mere "restatement," but the basis for a new doctrine, and deserves to be treated as such. For Nafe there need be no specific fibres within a given sense, but only a shifting flux of impulses arriving at the brain dispersed both in time and space. Under such a dispensation each fibre may in its time play many parts, and the fragment of information which it transmits has no sensory significance unless it is integrated with the information provided by the remainder of the whole company of fibres in action. Thus activity in a given fibre could at one time contribute towards the experience of a sensation of touch, and at another towards the experience of pain, cold or warmth. This idea of patterns of excitation is similar to that put forward by Lanier, Carney and Wilson (1935), Bishop (1946), and Clark (1947), and it has gained considerably in force by recent work on the innervation of the skin and on the excitation of the somatic sensory cortex.

Here, then, we have two contrasting viewpoints from which to survey the problem of cutaneous sensation—the "specific fibre" theory and the "pattern" theory. In order to evaluate their present-day status we must consider the development of several lines of research.

Anatomy and Physiology

(1) *Nerve-endings.*—At the time when von Frey formulated his theory four distinct types of sensory "spot" had been discovered in the skin, and four main types of cutaneous sensory ending had been described. It was therefore not surprising that he should arrive at the concept of four "modalities" of sensation, and that the term "modality" should become tacitly accepted as meaning a sensation for which there existed a specific nervous apparatus terminating in a specific type of nerve-ending. However, after 1894 improvements in technique resulted

in a great increase in the number of morphologically identifiable end-organs, so that Ruffini (1905) remarked: "tandis qu'avant cette époque les fonctions étaient beaucoup plus nombreuses que les formes, aujourd'hui, par contre, celles-ci ont pris leur revanche sur les premières."

Von Frey matched his four kinds of end-organ with his four sensory modalities on the basis of evidence which would have seemed totally inadequate had it not been published in German and with the weight of von Frey's authority. Nevertheless his allocations were susceptible of experimental investigation, and much effort was subsequently put into the hunt for end-organs—particularly those related to warm and cold. In spite of this, all attempts to establish a consistent relationship between marked sensory spots and the underlying histology have proved unavailing (*see* Hagen, Knoche, Sinclair and Weddell, 1953). It is for this reason that von Frey's suggestions have for the most part been discarded by experimental psychologists (Boring, 1942; Kantor, 1947; Jenkins, 1951), though they still persist in medical literature.

It has been shown that temperature sensibility is adequately represented in the pinna of the ear, where there appear to be no organized endings of any kind (Sinclair, Weddell and Zander, 1952), and that in the lip the temperature thresholds of the mucosa, which contains numerous organized endings, are similar to those of the skin margin, which contains none (Hagen *et al.*, 1953). Lele and Weddell (1955) later found that thermal sensations, as well as touch and pain, can readily be elicited from the centre of the cornea, where there are only free nerve-endings (Zander and Weddell, 1951). In association with this comes the suggestion (Tyrrell, Taylor and Williams, 1954) that free nerve terminals are well adapted to act as thermal receptors. The heterogeneous morphology of cutaneous endings does not support the association of functional and morphological specificity (Ruffini, 1905; Hagen *et al.*, 1953; Weddell, Pallie and Palmer, 1954), and Lele, Weddell and Williams (1954) have brought evidence to suggest that "the unencapsulated nerve endings in the skin, when suitably stimulated, can give rise to a wide range of sensory experience which includes reports of 'cold,' 'touch,' 'warm,' 'prick,' 'itch' and 'sharp pain'." They conclude that the facts can be better explained from a non-specific viewpoint than by the thesis that there are specific nerve terminals for specific sensory modalities.

It appears certain that von Frey's original allocations must be rejected. It still remains possible that specific endings exist, but that the differences between them are too subtle for our present investigative

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methods to detect. But it seems more likely that one and the same type of ending can mediate different forms of sensation according to the physical conditions to which it is exposed. Müller's idea of "specific irritability" must thus return to the status of a theory whose truth remains to be demonstrated.

But if we doubt the existence of specific terminals, what are we to make of the cutaneous sensory spots? These spots are mapped out by stimuli so small as to be "unphysiological" in the sense that they are unlikely to be encountered by skin which is not taking part in an experiment. Guilford and Lovewell (1936) explored patches of skin with touch stimuli of varying intensity and found that the proportion of points giving a response increases with the stimulus intensity. They conclude that "the traditional cutaneous 'spots' are largely fiction. We may be justified in speaking of 'gradients of sensitivity' but not of 'spots.' Such 'gradients of sensitivity' are probably a property of the distribution of sensitivity of the cutaneous receptors, some receptors having lower thresholds than others . . . An increased intensity of the stimulus probably has three effects, namely: (1) additional receptors with higher thresholds are brought into play; (2) the frequency of impulses in receptors already acting is increased; (3) due to the mechanical gradient set up by the stimulus, a wider area of tissue is affected and more receptors are brought into play." These findings in relation to "touch spots" are paralleled by the work on temperature spots of Heiser (1932) and Jenkins (1939*a*, 1939*b*; 1941*a*, 1941*b*). The number and position of temperature spots in a given area may vary considerably on successive examinations (Waterston, 1923), and Bing and Skouby (1949) have shown that the number of reacting cold spots can be very greatly increased by altering the skin temperature. Later (Bing and Skouby, 1950), they found that an increased concentration of acetyl choline in the skin has a similar effect. It thus appears that at any one time only a fraction of the total reactive surface responds to a given stimulus. Herring (1923) has suggested that this is a general property of cutaneous innervation dependent on the extensive branching of nerve fibres in the skin. However this may be, one might readily imagine that the fluctuating sensitivity of the skin overlies a fluctuating activity in an undifferentiated cutaneous network. On the other hand, orthodoxy would require in every area of skin a dense undergrowth of functionally distinct specific endings, the majority of which would be "resting" at any given time. Such an arrangement has yet to be demonstrated.

(2) *Nerve fibres.*—While we may confidently reject von Frey's detailed explanation of specific irritability and seriously suspect the

whole concept of peripheral neural specificity, this does not affect the question of specific energy and the theory of specific nerve fibres. The early critics of Müller's theory supposed that functional distinctions between different types of nerve fibre ought to be reflected in detectable morphological differences. But in spite of much histological work since Müller's time it has never been suggested that several structurally distinct types of nerve fibre can be found in cutaneous nerves. The impulses conducted along every fibre appear qualitatively similar, and the all-or-none law has further stereotyped the information passing to the central nervous system.

It has, however, been firmly established that nerve fibres vary more or less continuously in size and degree of myelination, and that this is connected with their rate of conduction of impulses (*see* Young, 1942). In the circumstances it is not surprising that attempts to correlate size and conduction velocity with sensory function have been prominent in cutaneous sensory physiology since electronic methods advanced sufficiently to allow precise investigation of sensory impulses.

(*a*) *Direct recording.*—Among the first to use these methods was Adrian, who led off from frog and cat nerves after applying various stimuli to the skin. In summarizing this work (Adrian, 1931) he suggested that the receptors for light touch were supplied by larger medullated fibres, and that pain might be mediated by fibres giving very small potentials. Later, however, he stated ". . . there is no escape from the conclusion that both medullated and non-medullated fibres are responsible for pain . . . for all we know the smaller medullated fibres may give both contact or pain according to the magnitude of the discharge" (Adrian, 1932).

In 1936 Zotterman made an important contribution by recording from the sensory nerves supplying the tongue of a cat. In response to a touch stimulus the action potentials were large and rapidly propagated; with stimuli which might reasonably be supposed to give rise to pain small slow potentials appeared. The application of drops of water at various temperatures produced potentials with intermediate characteristics. These observations initiated a series of papers by Zotterman and his associates, most of which have been reviewed by Zotterman (1953). By repeatedly splitting the nerves from which recordings are taken, it is possible to obtain a preparation which gives a reproducible spike when a drop of cold water is put on the tongue. The electrophysiological behaviour of this preparation differs from that of others in which an identifiable spike discharge is fired off when a drop of warm water is applied. The only other anatomical situation

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in which these results have as yet been duplicated is the glabrous skin of the cat's nose (Hensel, 1952), but Zotterman is in no doubt about what he has found. He maintains that the spikes occur in specific "cold fibres" and "warm fibres" which lead from specific thermal receptors in the tongue. Nevertheless, in these experiments, as in most electrophysiological sensory work, there is no histological proof that the spike is derived from a single fibre, and it is possible that several fibres are being fired synchronously. When the cat's cornea is used as the test area the electrophysiological results are not inconsistent with the hypothesis that one and the same nerve fibre may respond to cold or to radiant heat (Weddell, 1955*b*). It has indeed been claimed that Zotterman's findings, far from supporting the idea of sensory specificity within the quality of temperature, are in favour of a theory which holds that both cold and warm sensations result from the arrival at the brain of a pattern of impulses aroused in a common plexus of undifferentiated endings in the periphery (Lele, Weddell and Williams, 1954; Weddell, 1955*a*).

All experiments on animals suffer from the defect that the animal cannot describe its sensations, and the work of Heinbecker, Bishop and O'Leary (1932, 1933) on man is thus important. By stimulating sensory nerves in conscious patients they were able to elicit sensations of pain and touch, but not of temperature; alterations in quality could be produced by altering the frequency but not by altering the strength of stimulation. In one patient the nerve stimulated was examined after amputation, and the threshold stimulus for pain was found to be just adequate to elicit a threshold response of the "second potential" from myelinated fibres of the "visceral afferent" group. Later (1936) they conclude that: ". . . while minor differences exist, it is proper to state that in any given respect a human nerve is practically identical in its general composition and function with the corresponding nerve of some animal." They believe that in man "pain from stimulation of the myelinated fibres is so overpowering that any additional effect of pain from the non-myelinated fibres cannot be appreciated." Pattle and Weddell (1948) used condenser discharges to stimulate a human digital nerve; they obtained two types of pain from fibres which they considered were of small diameter.

Weddell, Taylor and Williams (1955) have recently demonstrated that in the rabbit's ear the stimulation of a single hair will result in impulses passing up several different fibres in the nerve trunk which leaves the ear. The fibres involved can be of different sizes and thus of different conduction rates. They point out that the stimulation of a

single hair is a wholly unnatural occurrence in everyday life, and that the pattern resulting from a more physiological tactile stimulus must be even more complex. The inference is that activity in a single fibre is an unnatural event, and we have no evidence that it can occur in the intact body, or, if it does occur, that it can ever result in a sensation being perceived. So far it has not proved practicable to record from a single human fibre to decide the second part of this inference, but such an experiment would seem to be essential if we are to claim that specificity is a function of the characteristics of a given type of nerve fibre rather than the result of the firing of a given type of pattern among a whole group of reacting nerve fibres. Meanwhile, electrophysiologists are now cautiously speaking of "impulses aroused from low-threshold cutaneous receptors" where once they might happily have talked about "touch impulses."

(*b*) *Reaction times.*—There is a definite interval between the time of application of a cutaneous stimulus and its perception. The "perception time" cannot be directly measured, but estimates of its magnitude are commonly made by measuring the time which elapses between the application of the stimulus and the completion by the subject of a prearranged response. This interval is known as the "reaction time," and clearly any differences in the reaction times for different modalities are relevant to the theory of sensory specificity.

From the first it was recognized that reliable figures are hard to obtain (Wundt, 1904), but on the face of it the experiments required are simple ones, and soon became familiar to all students of psychology and medicine. It is agreed that the reaction time is the sum total of many shorter times; the time taken for initiating conduction, for conduction itself, for perception and judgment, for synaptic crossings, and for traversing the efferent pathway (Monjé, 1934; Michon, 1939). It has generally been assumed that the only part of the complex which can vary to any considerable extent is the conduction time, and in this way estimated conduction velocities appropriate to different modalities have been obtained. For example, a touch stimulus applied to a toe has in general a longer reaction time than a similar stimulus applied to a finger. By measuring the relative distances of the toe and the finger from the central nervous system it is possible to derive a figure which purports to represent the "conduction velocity of touch." But Lele, Sinclair and Weddell (1954) have recently shown that equally large differences in reaction times may be obtained by stimulating two adjacent areas on the finger tip. Clearly conduction time cannot be the only variable. Wright (1951) and Piéron (1952) divide up the reaction time into a variable part

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and a fixed part. But even if we knew the value of this irreducible minimum, it would remain uncertain how the component delays were distributed within it.

In all four "modalities" the reaction time can be grossly influenced by the intensity of the stimulus (Dolley and Cattell, 1894; Kauffmann, 1921; Piéron, 1929; Eichler, 1930; Piéron and Segal, 1938; Wright, 1951; Lele, Sinclair and Weddell, 1954; Lele and Sinclair, 1955). In addition, it has been shown that tactile and thermal reaction times vary from day to day and from subject to subject (Lele, Sinclair and Weddell, 1954; Lele and Sinclair, 1955), and that pain reaction times vary according to the type of noxious stimulus (Piéron, 1929, 1930, 1931). It has been suggested that such variations are due to central rather than peripheral delays (Kauffmann and Steinhausen, 1921; Piéron, 1929, 1930, 1931), and a similar explanation has been put forward to account for the delay in perception of stimuli in clinical cases of hypoæsthesia (Stein and von Weizsäcker, 1927).

The interval between stimulus and perception is not necessarily the same for all modalities. Thus, everyone who has stubbed his toe knows that under these circumstances touch is perceived before pain. However, it does not follow that the impulses making up the message which the brain will ultimately interpret as "touch" must travel faster in the peripheral nerve than those making up the "pain message." We cannot assume that the central process required to translate a series of impulses into the sensation of touch takes the same time as the process required to translate another series into the sensation of pain. Nor, indeed, can we be certain that the time taken for stimuli applied to the skin to arouse impulses in the peripheral nerve fibres is of the same order for all modalities. In other words, we cannot make any legitimate comparison between different modalities in respect of conduction velocities if we base our argument on the evidence of reaction times; we cannot say that "touch" travels faster than "warm" or "pain." It is perhaps not sufficiently realized that we still know almost nothing of what happens at either end of a chain of sensory nerve fibres.

(*c*) "*Second pain*": Under suitable conditions, a double sensation of pain may be obtained in response to a single stimulus. Thunberg (1902) suggested that the second component of the double response resulted from some chemical process which needed time to develop, and this view was supported by Lewis and Hess (1933), who suggested that the first component was due to physical or physico-chemical action on the nerve-endings, while the second was the result of some metabolite (other than histamine) being liberated by tissue damage. Others (Rosenthal and

Minard, 1939; Rosenthal and Sonnenschein, 1948; Rosenthal, 1949) have since brought evidence in support of this idea, though they suggest that Lewis and Hess were wrong to exclude histamine as a chemical mediator. However, Lewis changed his mind when he and Pochin (1937) found that second pain could not be elicited from certain areas of the body, and that in the remainder the delay in appreciation of second pain appeared to vary directly with the distance of the test site from the central nervous system. These findings clearly did not fit the concept of a chemical intermediary very well, and Lewis and Pochin concluded that there must be two sets of "pain fibres" in peripheral nerves, each conducting at a different rate. The greater the distance of the test site from the brain, the greater the separation in the time of arrival of the two sets of messages. Conversely, when the distance from the brain was reduced below a certain limit, it was no longer possible to distinguish the separation. They used a thermal stimulus, but their measurements of reaction times take no account of the comparative thresholds of the areas stimulated or of their skin temperatures. In view of the recenf observations of Lele (1954), Lele, Weddell and Williams (1954) and Lele and Sinclair (1955) on the importance of these factors in the genesis of sensation by thermal applications we ought perhaps to consider these measurements as standing in need of confirmation. Again, if the phenomenon of second pain depends on the existence of two sets of pain fibres it is curious why a thermal stimulus is so much more effective than a prick in eliciting it. Lewis and Pochin failed to obtain second pain from the face by a thermal application, but they observe in a footnote that a delayed painful sensation—which they distinguish from second pain on not altogether satisfactory grounds—can occur when the face is pricked. Further, they take no account of the varying density of innervation in the test sites they used, though this might have a considerable bearing on the efficiency of a diffusing chemical intermediary.

Lewis and Pochin supported their interpretation by recourse to compression of a limb. During compression blocks of peripheral nerves the delay between the application of a painful stimulus and its perception is characteristically increased, as indeed occurs in all modalities (Sinclair and Hinshaw, 1951*b*). Lewis and Pochin identified this delay with the delay in the perception of "second pain" when normal skin is stimulated. The figures they cite are, however, quite inadequate to support this identification (Sinclair and Hinshaw, 1951*b*). Wortis, Stein and Joliffe (1942) also worked with cuff blocks, and agree with their conclusions, though they stress the inaccuracy of the method. From these experiments it has come to be generally assumed that the two hypothetical sets of

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pain fibres are differentially affected by blocking, and that the delayed pain sensation which is all that can be elicited in the later stages of a compression block is of the same nature as normal "second pain" which has been in some way unmasked by the removal of the faster group of fibres. However, Sinclair and Hinshaw (1951*b*) have observed delays in cuff experiments which are much greater than could be accounted for by conduction in any type of sensory fibre now thought capable of conveying "pain impulses" (Erlanger and Gasser, 1930; Adrian, 1932; Gasser, 1950). Landau and Bishop (1953) use the fact that two varieties of pain can be separated by a cuff block to support Head's theory of two distinct sets of pain fibres in the skin, but do not rely on measurements of delay. Pochin (1938) brought evidence to show that the delay in perception of pain in tabes dorsalis is very similar to the delay in the perception of "second pain" in normal subjects, and explained this by suggesting that in tabes the faster fibres are destroyed, leaving the slower ones still conducting. His results may be criticized on the grounds that he used stimuli of grossly different intensities for the tabetic and the control groups. In any case, as Ashby (1949) points out, there are many recorded instances of much longer delays in tabes, some of which are too great to be accounted for by Pochin's explanation.

Gordon and Whitteridge (1943) measured the interval between the application of a painful stimulus and the resulting disturbance of the electroencephalogram, and deduced conduction times for "first" and "second" pain fibres. If the only possible reason for this interval was a difference in conduction rates, this experiment would be valuable, but as matters stand it begs the question, since it tells us nothing about what is happening in the periphery. It is interesting that Powell and Cowan (1955) have found that in animals the time elapsing between stimulus and consequent cortical disturbances varies inversely with stimulus intensity.

The question of second pain thus cannot be regarded as settled, and the idea of two sets of pain fibres rests upon work which is not immune from criticism of the experimental findings as well as the interpretations placed upon them. It would seem essential to reinvestigate the problem in the light of more recent knowledge.

(3) *Central terminations.*—Müller suggested that the specific energy of the nerves subserving the five senses is related to their central terminations, and if his doctrine is to be extended to apply within the cutaneous sense it is to the central terminations of the cutaneous afferents that we should look for enlightenment. Yet this is the part of the sensory path-

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way about which we know least, though evidence is rapidly accumulating through the efforts of the electrophysiologists.

It has long been known, from anatomical and clinical evidence, that there exists some sort of rough "map" of the body surface in the primary somatic sensory area of the cerebral cortex. In 1937 Marshall, Woolsey and Bard succeeded in recording from this area the electrical disturbances produced by stimulation of different parts of the body, and since then many electronic maps have been made of the area in different animals, using tactile stimuli or electrical excitation of different sensory nerves. It is now thought that even minimal tactile stimulation of a given point on the skin always leads to responses from an *area* of cortex rather than a point, and that this area overlaps the representation of adjacent body regions. It thus seems unlikely that localization of a stimulus on the body surface can be associated with activity in a given cortical cell, and it is more probable that localization "must depend on the assessment of afferent data in a cortical area of appreciable size" (Adey, Carter and Porter, 1954).

We have as yet no maps of the primary sensory somatic area made in response to thermal or painful stimulation, but it is well known that there is some difficulty about pain, and thermal sensibility, though not so often discussed, is in similar case. It is still uncertain whether the cortex has any primary role in the *perception* of pain, though the results of frontal leucotomy leave little doubt that it has an important role in its *appreciation*. Head (1920) is responsible for the widely held belief that the thalamus is the place where pain enters consciousness, but Kleist (1922) has suggested that pain is indeed represented in the somatic sensory area, and this view has considerable support (Marshall, 1951). Russell (1945) and Marshall (1951) have recently put the case for cortical representation of pain, basing their views on the clinical results of brain injuries. Lewin and Phillips (1952) report instances of intractable pain which at operation could be reproduced by stimulating the cortex of the post-central gyrus, and was subsequently relieved by ablation of the appropriate area. Against this must be set the facts that some patients after hemispherectomy retain a very considerable power to appreciate pin-prick on the opposite side of the body (Walker, 1943), and that stimulation of the cortex very seldom yields pain in a normal subject (Penfield and Boldrey, 1937). The former objection may merely indicate bilateral sensory representation in the cortex (Woolsey and Fairman, 1946), and the latter may not be relevant, since the cortex does not normally deal in incoming stimuli of the type inflicted on it by the neurosurgeon (Walshe, 1951). On the whole, therefore, the

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evidence appears to favour the view that there is some relationship between the somatic sensory cortex and pain sensibility. With regard to the other cutaneous modalities, the situation has not progressed so far, though there is now evidence that impulses aroused in the deeper tissues are ultimately conveyed to the same general region as those derived from the skin (Adey, Carter and Porter (1954)).

If, as seems possible, the impulses aroused from cutaneous stimulation all make for the same geographical area of cortex, the crux of the problem is to discover whether there is any evidence of functional segregation within that area. It is implicit in the theory of von Frey that there should be a point-to-point localization of sensory function in the cutaneous receptive area, and thus that in the region corresponding to each part of the body there should be four mechanisms adapted to the specific reception of touch, cold, warm and pain. There must, in fact, be both topographical and functional representation of every part of the skin (Ruch, Patton and Amassian, 1952). On clinical evidence Kleist (1922) concluded that pain and temperature are represented in the anterior part of the area, and similarly Russell (1945) and Marshall (1951) found that injury to this region resulted particularly in a loss of pain and temperature sensibility. There is as yet no anatomical basis for such a suggestion, though Le Gros Clark and Powell (1953) have found differences in the type of connexion made by the thalamus with areas 1, 2 and 3 of Brodmann in the macaque.

While, therefore, the von Frey theory might explain satisfactorily the capacity of the brain to localize cutaneous stimuli, it is not, as yet, particularly happy in its explanation of the capacity to recognize quality. The pattern theory, on the other hand, finds no difficulty in relating the quality of the sensation experienced to the characteristics of the pattern which can be detected arriving at the cortex, but is not so ready to explain localization. Adey, Carter and Porter (1954) have suggested that the temporal dispersion of the pattern may be a factor in localization, and this emphasizes the way in which modality and locality seem to be inextricably bound together, whether in a scheme depending on patterns, or in one dependent on specific terminations. It is fair to say that the evidence is as yet insufficient to favour one theory or the other.

Pathology and Surgery

(1) *Reversible blocks of peripheral nerves.*—Three methods of blocking cutaneous nerves—cooling, compression, and the use of chemicals—have been applied by a large number of people to the analytical study of cutaneous sensation (*see* Sinclair and Hinshaw, 1950*a*, 1950*b*, 1951*a*,

1951*b*). Other blocking agents have not as yet been fully explored : one may mention as an example the application of faradic stimulation to peripheral nerve trunks by Shawe (1924) and Thompson and his colleagues (Thompson, 1935; Thompson *et al.*, 1934; Thompson, Luce and Denny, 1948).

By the end of the nineteenth century it had been established that in blocks of this kind there is a tendency for the responses to different kinds of stimuli to disappear successively rather than simultaneously, and that the order in which the four recognized sensory modalities fail differs according to the blocking agent used. Barker (1896) suggested that there might be a spatial segregation of modalities in the nerve trunk, the bundles of fibres subserving each differing in their accessibility to the attacking agent. This explanation failed to find favour, and indeed observation of partial lesions of sensory nerves has lent it little support (Bowden and Napier, 1955). It was easier to suppose, along the lines suggested by Dixon (1905), that the specific fibres mediating each modality were of differing susceptibility to the blocking agent, and so failed at different times. The argument was so clear that many investigators turned their attention to establishing the time of failure of subordinate sensations like tickle or itch in order to discover their relationships to the four main modalities. It was not until 1929 that the development of electrophysiological techniques made possible a new approach to the human sensory work.

In 1929 Gasser and Erlanger excised sensory nerves from frogs and mammals and exposed them either to pressure or to the action of cocaine. They were able to show that in general the fibres ceased to conduct in a sequence roughly correlated with their size, the order being different in the two types of block. They suggested that fibre size might be a factor in determining the way in which sensory modalities failed in compression and chemical blocks in man though they noted some discrepancies in the psychophysiological literature. Others were not so cautious (Ranson, 1931, 1933; Gerard, 1931), and it was largely as a result of this work that the idea gained ground (little of which has since been lost) that touch is an affair of the large fibres and pain an affair of the smallest, with temperature occupying a somewhat uncertain intermediate position. This view has to encounter several objections.

It is extremely difficult to reconcile the human and animal findings into a consistent scheme, and the original suggestion has become progressively more attenuated in successive presentations by Gasser himself (1935, 1943, 1945.) He concludes (1943) that: "the fibres belonging to different modalities must be widely distributed throughout

the various fibre sizes, and . . . there seems to be little possibility of associating any one sensation with an elevation in the electroneurogram." The work of Sinclair and Hinshaw (1950*a*, 1950*b*, 1951*a*, 1951*b*) has shown that in procaine blocks in man it is possible to obtain almost any desired order of sensory loss by using different experimental subjects, by varying the site stimulated, or by altering the characteristics of the stimuli. In compression and cold blocks the results are similar, though the variation observed is not quite so great. It is thus meaningless to say, for example, that in a given block pain fails before touch unless what is meant by "pain," "touch," "fail," and "before" is rigidly defined. If narrow definitions of this kind are applied to the stimuli and end-points, it is possible to show that in each of the three types of block statistically significant differences in the order of sensory loss can exist between one subject and another, between one nerve territory and another, and even between different parts of the same nerve territory. For this reason no comparison between the sensory dissociations produced by different agents can be valid unless it is made on the same sites in the same volunteers under identical experimental conditions, and much of the confusion in the literature is probably due to a failure to specify the experimental conditions.

Nevertheless, by adopting a controlled experimental technique Sinclair and Hinshaw (1950*b*, 1951*a*) were able to demonstrate statistically significant differences between the orders of sensory loss in the three different types of block. Clearly the order of loss is not entirely an artefact produced by our selection of experimental conditions, but—at least in part—depends on some specific effect of the agent.

Much of the trouble experienced in fitting the human to the animal results is connected with temperature sensation. The response to a thermal stimulus of constant temperature varies radically according to the skin temperature at the time (Lele, 1954; Lele, Weddell and Williams, 1954; Lele and Sinclair, 1955). During any kind of block the skin temperature alters progressively, and in cold blocks it may change suddenly and dramatically. Yet in none of the work on sensory dissociation has there been any standardization of the stimulus by relating its temperature to that of the skin. It is therefore perhaps not surprising that "warm" and "cold" should occupy very varied positions in the recorded order of sensory loss, and we may reasonably neglect the temperature findings pending further information. If this is done, the picture clears a little. In the literature pain fails before touch in procaine blocks and after it in compression blocks. In general, the animal results show that small fibres fail before large in procaine

blocks, and after them in compression blocks, though the process is not always uniform (Gasser and Erlanger, 1929; Heinbecker, Bishop and O'Leary, 1934; Bishop and Heinbecker, 1935). We might therefore suppose that touch is carried by large fibres and pain by small. But in procaine blocks of the lateral popliteal nerve touch fails before pain, and to explain this discrepancy we should probably have to conclude that the cutaneous branches of the lateral popliteal nerve contain relatively few large fibres. There appears to be no anatomical evidence in support of this proposition, and the technique required to establish it presents some difficulties (Sunderland, Lavarack and Ray, 1949).

It is also probably important that in cold blocks motor power and vasomotor tone commonly disappear almost concurrently, and long before touch (Bickford, 1939; Sinclair and Hinshaw, 1951*a*). It is accepted that many of the motor fibres and some of the fibres subserving touch are large, while the vasomotor fibres are small. It therefore appears possible that in man cooling can produce a sensory dissociation, qualitatively similar to that produced by procaine or compression, in which the fibres do not fall out on the basis of their size. Yet cooling produces a stable order of sensory loss. Electrophysiological studies of cold blocks show that the smallest fibres survive longest (Gaze and Gordon, 1954), as in compression blocks, but under standard conditions a significant difference in the relationship of touch to pain can be demonstrated between the two types of block (Sinclair and Hinshaw, 1951*a*).

On the whole, therefore, it seems that we must accept with some reserve the suggestion that fibre size is the dominant factor in the production of sensory dissociation in experimental nerve blocks, though it may be suspected of exercising a considerable influence. We have no evidence that any other factor determines the differential susceptibility of specific sensory fibres to different blocking agents.

The pattern theory has to face similar difficulties in regard to fibre size. The pattern of a given sensation depends on the spatial and temporal dispersion of impulses within the nerve trunk. Knocking out a proportion of the fibres in the trunk must inevitably alter the characteristics of the patterns which can still be conducted, and so could produce a sensory dissociation. Different agents must produce different sequential changes in the patterns, or there would be no differences in the order of sensory loss in the various kinds of block. There is nothing to suggest that it is the spatial aspect of the pattern which is attacked, and the only plausible explanation is that the fibres are differentially susceptible to these agents on a size basis. We must therefore conclude that fibre size

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is a major factor in the pattern theory of dissociation. For example, it is probable that for a pattern to be recognized as "touch" it must contain a large proportion of rapidly conducted impulses; pain, on the other hand, might require the assistance of many small fibres. We cannot, therefore, escape the objections raised to the specific fibre theory. It is possible that some of these objections are to be explained by the differences between *in vitro* and *in vivo* experiments (Sinclair and Hinshaw, 1950*b*, 1951*a*), and it is certain that more work is necessary before the situation can be clarified.

(2) *Peripheral surgical blocks.*—(*a*) *Section of peripheral nerves:* It is easy to demonstrate, by cutting or blocking cutaneous nerves, that the territory of a given nerve is overlapped by those of its neighbours. There appear to be no abrupt changes in the density of innervation of the skin where one nerve overlaps another, and it follows that in any one nerve territory the peripheral overlap zone must be less densely innervated than the central autonomous zone. If a nerve is cut, there will thus be a central area of complete denervation, surrounded by an annulus of sparsely innervated skin which in turn abuts on innervation of normal density. It is a widely accepted clinical observation that under these circumstances there is a spatial dissociation of sensibility, the area of analgesia being smaller that the area of anæsthesia (Bowden, 1954). Nevertheless Cobb (1919) found that the area of analgesia could be made larger or smaller than the area of anæsthesia merely by varying the weight on the testing needle. He concludes: "Dissociations of sensation due to peripheral nerve lesions arise from comparing stimuli not only qualitatively different but quantitatively unequivalent. In short, they are artefacts." In spite of this forceful statement, it has come to be accepted that the spatial dissociation is a real phenomenon having an existence independent of the testing methods used. This has never been proved, and it remains possible that "dissociation" occurs simply because the overlap zone is an annulus of gradually decreasing density of innervation. A heavy prick will thus register a boundary nearer the anæsthetic zone than a light one, and similarly with touch stimuli. It may be that where innervation is thinnest a prick is at an advantage over a touch stimulus because of the intervention of a diffusing chemical intermediary (Rosenthal, 1949).

If, however, the dissociation is real, the pattern theory could explain it if we suppose that the perception of touch requires a denser pattern of impulses than the perception of pain, so that the zone of reduced innervation is thus more sensitive to pain than to touch. On the specific fibre theory the position is more complicated. The usual explanation

is that the overlap of pain fibres between adjacent nerves is greater than the overlap of touch fibres. Now there are no signs of increased sensitivity to touch or pain as we pass from one nerve territory to another, and the density of pain and touch innervation is thus presumably fairly uniform. The concept of differential overlap thus implies that the autonomous touch zone must be larger than the autonomous pain zone, and it follows that the gradient of sensitivity in the touch overlap zone must be steeper than the gradient in the pain overlap zone. Accurate data on this point are lacking.

(*b*) *Section of posterior nerve roots:* Lesions of posterior nerve roots have not been so extensively studied as lesions of peripheral nerves. The overlap of adjacent dermatomes appears to be much more complete than the overlap of adjacent nerve territories, and indeed Foerster (1933, 1936) states that section of one posterior nerve root never gives rise to a sensory loss which can be detected by ordinary clinical methods of sensory examination. This has since been denied (Keegan, 1943; Keegan and Garrett, 1948), but there is still considerable controversy over the exact boundaries of sensory disturbance when these are mapped by different methods (Kuhn, 1933; Haymaker and Woodhall, 1953), and this at least indicates that the problem is not a simple one.

Foerster (1933, 1936) overcame the difficulty by cutting a number of roots both below and above the one he wished to investigate—the method of "residual sensibility" first employed by Sherrington in monkeys. In the course of this work he observed that in a given dermatome the area sensitive to touch is greater than the area sensitive to pain. This finding—the reverse of conditions in the nerve territory—is very difficult to account for. Weddell (1941) presents two clinical cases of subtractive root lesions to support Foerster's findings, and argues that the difference is due to the large amount of overlap in root territories and "the smaller area supplied by the terminal ramifications of fibres subserving touch as compared with those subserving pain." It is clear that the greater degree of overlap means that the gradients of sensitivity across the dermatome will be more gradual than the gradients across the peripheral nerve territory, and this would add to the difficulty of establishing a precise boundary for either touch or pain. But it is not easy to see how the degree of overlap could *reverse* the clinical findings. Again, the area supplied by a touch or pain fibre does not change because the fibres regroup themselves on their way to the central nervous system, and arguments applied to the size of terminals of fibres in a nerve trunk must apply with equal force to the size of terminals of fibres in a posterior root. Nevertheless, if we assume that in a given

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area of skin there are more individual touch terminals than pain terminals, it is possible to demonstrate by means of a diagram that this arrangement, coupled with the greater overlap of pain fibres between adjacent trunks, could lead to the clinical results recorded. There is no anatomical basis for this assumption. Similarly, the pattern theory can offer no easy explanation of the clinical findings.

But it may be that there is no discrepancy to explain, and that we are dealing with one of Cobb's "artefacts." The boundaries of touch and pain sensibility in the illustrations given by Foerster and Weddell are usually very close together, and occasionally cross each other. In few pictures is the separation between the two modalities wholly convincing. There do not seem to have been any control observations on the contralateral side of the body. Weddell's boundaries can hardly be accepted with confidence in view of the known difficulty of reproducing sensory boundaries in such cases when different methods are used. Foerster's method is not so open to this objection, but he gives no adequate account of his testing procedures. It is unlikely that his technique will ever be used again, and thus the elucidation of this point may well remain obscure.

(*c*) *Regeneration of peripheral nerves:* During regeneration of a sensory nerve, sensory dissociation is a characteristic feature, and is both spatial and temporal. Accidental nerve injuries seldom involve people who are gifted sensory witnesses, and, moreover, they do not allow of proper control observations. It was for this reason that Head decided to study the return of sensation to a deliberately denervated area of skin on his own forearm (Head, 1905; Rivers and Head, 1908). He found that the first type of sensibility to return was an ability to recognize extremes of temperature and pain, and this he termed "protopathic sensibility." Later, as recovery proceeded, the area began to respond to light touch, and to be capable of discriminating between more moderate temperatures and of localizing tactile stimuli. This finer type of sensibility Head called "epicritic." He postulated that there were two distinct systems of nerve fibres, having different rates of regeneration; the "protopathic" system outstripped the "epicritic" system as both grew in towards the centre of the denervated area. A full account of this theory is given by Head (1920).

However, none of the investigators who subsequently performed similar experiments (Franz, 1909; Trotter and Davies, 1913; Boring, 1916; Sharpey-Schafer, 1927, 1929; Lanier, 1935; Lanier *et al.*, 1935) confirmed the experimental findings essential to the structure of the theory. Further, the results of the examination of the plentiful crop

of nerve injuries in the first world war were also inconsistent with Head's results and theory (Stookey, 1916; Burrow, 1919; Pollock, 1919; Cobb, 1919; Frazier and Silbert, 1920), and though some support was still forthcoming for the protopathic-epicritic theory (Ranson 1915; Stopford, 1926, 1927; Adrian, 1931; Landau and Bishop, 1953), the position has generally been considered untenable since the last full discussion of the matter in a critical review by Walshe (1942).

After Head's important study more attention was paid to the question of protopathic and epicritic sensation than to the order of return of the four more usually recognized modalities of sensation in nerve injuries. As in the experimental nerve blocks, there has been little attempt to standardize stimuli or experimental conditions, and the very nature of the problem makes any such attempts very difficult. Young (1942) gives the usual order of sensory return as pain, touch, cold, warm, but he notes that there is "considerable disagreement," and one reason for this must undoubtedly be the use of different stimuli by different observers (Cobb, 1919). Nevertheless, it is fairly generally agreed that pain—or at least, response to pin-prick (Napier, 1952)—is the first sensation to return to the anæsthetic area, and that this is followed later by touch and temperature (Napier, 1955). For reasons which have already been discussed, little reliance should be placed on the positions allotted to cold and warm sensibility, and until thermal stimuli controlled by skin temperatures are adopted we have only to explain the relative position of pain and touch. The dissociation is usually ascribed to a differential rate of growth of the specific nerve fibres subserving the two modalities, the pain fibres growing faster. The concept is so simple that it is rarely questioned, but it remains pure hypothesis. There has been a considerable amount of work on the maturation of fibres in regenerating nerves (Gutmann and Sanders, 1943; Young, 1942; Aitken, Sharman and Young, 1947; Young, 1948), but most of the effort has been directed towards motor rather than sensory trunks. However, we may reasonably assume that the findings apply also to cutaneous nerves. In the nerve trunk the first fibres to reach their destination are thin, and only after some considerable time does the nerve approach its normal fibre spectrum. This would fit well with the finding that pain is the first sensation to return, and might be taken to support the specific fibre theory.

But the pattern theory could explain the facts equally well. At first the innervation in the skin is sparse and composed of small fibres. As it approaches the normal condition, sensation gradually recovers, the apparent segregation into modalities being partly a function of the

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testing methods used, and partly due to the differing impulse patterns needed for the adequate perception of different kinds of sensation. It has already been suggested that the "touch pattern" requires the presence of more large fibres than the "pain pattern." The fact that territories of recovery to different forms of stimuli may be spatially distinct could be due to a localized increase in density of the innervation and a thickening of the nerve fibres draining it.

(3) *Central surgical blocks.*—Since 1911, when the first surgical section of the antero-lateral part of the spinal cord successfully relieved a patient of intractable pain (Spiller and Martin, 1912), many patients have undergone the operation of antero-lateral cordotomy, sometimes with dramatic success, sometimes with no improvement. In an attempt to reduce the number of failures the scope of the cut, at first restricted to the supposed position of the lateral spinothalamic tract, has been gradually increased till it includes more than half of the lateral column of white matter and a substantial proportion of the anterior column (White and Sweet, 1952; Kahn and Rand, 1952; Hamby, 1954: White, 1954). The best statement of the sensory results of such an operation is given by White, Sweet, Hawkins and Nilges (1950). In their experience complete insensibility to pain can be achieved with a minimal disturbance of touch sensation in the affected area, though they note changes in the touch thresholds. Notwithstanding the work of Stookey (1929), the majority opinion appears to be that pain can seldom be dissociated from temperature, though this occasionally occurs in disease (Sherman and Arieff, 1948). The distinction thus appears to be largely between touch on the one hand and temperature and pain on the other, and the sensory dissociations produced by section of the lateral spinothalamic pathway in the medulla (Schwartz and O'Leary, 1942) or mid-brain (Dogliotti, 1938) are of a similar nature (Walker, 1942*a*, 1942*b*).

It seems clear that throughout the length of the lateral spinothalamic tract the sensory fibres are segregated according to their place of origin, though there is considerable variation in the way they cross over, and cases have been reported in which antero-lateral cordotomy has led to ipsilateral pain loss only (White, 1954). In 1932 Foerster and Gagel suggested a topographical localization of function within the tract, "pain fibres" lying in a different region from "temperature fibres," and these again being positionally distinct from "touch fibres." Walker (1940) maintains that if such an arrangement exists it cannot be so clear cut as Foerster and Gagel suggested, since the clinical results show that "one modality is never involved to the exclusion of others." Never-

theless, he provides a diagram showing a rough secondary topographical segregation of functionally specific fibres superimposed on a map of fibres derived from different parts of the body. Direct evidence has recently been obtained by White (1954) and his colleagues, who have stimulated the antero-lateral region of the cord through electrodes inserted into it at operation. They obtain intermingled pain and thermal sensations, but do not report touch; they find no tendency for the painful sensations to become less frequent as the electrodes are pushed medially.

The accepted explanation of the dissociations produced by cordotomy and other operations such as intramedullary tractotomy of the fifth nerve (Sjöqvist, 1938) is that the "pain fibres" and "temperature fibres" have been severed, leaving the "touch fibres" intact because they travel up by another route. If this is so, the sensory organization of the spinal cord differs fundamentally from the sensory organization of the peripheral nerves which feed it. There is no suggestion that the interruption of a bundle of fibres occupying a given topographical position within a peripheral nerve can lead to sensory dissociation, though it is interesting that Hyndman (1938) claims it is possible to section the root of the fifth cranial nerve in such a way as to abolish the painful crises of trigeminal neuralgia while leaving a minimal sensory loss on the face. It may be that the organization of sensory roots is in some measure intermediate between that of the spinal cord and that of the peripheral nerves. Again, there is so far no evidence of any functional localization of specific sensations within the thalamus. Maps of the thalamus have been made in several animals by recording the electrical responses within it to tactile stimulation of the surface of the body (Mountcastle and Henneman, 1952; Rose and Mountcastle, 1952). Recently Gaze and Gordon (1954) have identified two types of unit in the thalamus, one corresponding to action potentials in large fibres of the peripheral nerve, and others which can only be aroused by stronger stimuli which are adequate to bring in smaller fibres. But they can detect no anatomical segregation between the different types of unit.

If specific pathways of specific fibres exist in the spinal cord, their anatomical situations and boundaries are ill-established. Petrén (1902), after reviewing the reported cases of damage to the spinal cord by injury or disease, concluded that there must be two main pathways for touch, one in the antero-lateral region, and another in the posterior columns. Bohm (1952) has shown that most of the impulses aroused in low-threshold cutaneous receptors seem to travel in the posterior columns and not in the antero-lateral region. White (1954) believes that much

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of the pain persisting after antero-lateral cordotomy must be due to impulses passing up the posterior columns, and the minimal effect of the operation on touch sensibility does not favour the existence of an important touch pathway in the antero-lateral region. The lateral spinothalamic tract itself is by no means as well-defined as could be wished, and may appear to peter out alarmingly before the thalamus is reached; indeed, it is stated that a direct spinothalamic connexion only exists in man and the primates (Glees, 1953). Gaze and Gordon (1955) investigated the thalamic responses to cutaneous stimulation in animals after destruction of various sectors of the spinal cord. They were unable to "allot impulses aroused by any particular kind of stimulus to one exclusive path, although . . . no responses other than tactile were shown to be mediated by the dorsal columns."

We are on surer ground if we neglect individual tracts and consider the distribution of fibre size within the white matter. Häggqvist (1936) analysed a cross-section through the spinal cord of a 13-year-old child by dividing it into zones and comparing the fibre spectrum of the myelinated fibres in each zone. In this case at least there was a very considerable difference between the spectrum for the antero-lateral region and that for the posterior columns. Other workers (Glees, 1953) have confirmed that the fibres in the antero-lateral region tend to show peaks in the smaller size-ranges, while those in the posterior columns are comparatively large (Lloyd, 1944). It has been known for some time that the maximal conduction velocities in the posterior columns are smaller than the maximal conduction velocities in peripheral nerves, and that therefore either a selection of neurons or a change in conduction properties occurs soon after the dorsal root fibres reach the posterior columns. Gasser and Graham (1933) ascribed the slowing of velocity to a decrease in diameter of the axons after giving off collaterals to the grey substance. Lloyd (1944) agrees with this interpretation, but suggests it is possible that the dorsal columns "contain significant selections from among the fibres of the dorsal roots."

Whatever the mechanism, we may accept the probability that the spectrum of fibres eliminated by antero-lateral lesions of the spinal cord will differ from that affected by lesions of the posterior columns. The facts thus admit of another explanation; instead of cutting specific pathways traversed by specific fibres, we may be so altering the sensory patterns the spinal cord is capable of conducting in such a way as to lead to a sensory dissociation. We have already postulated that the recognition of touch may require the activity of a relatively high proportion of larger fibres—such a spectrum as is found in the posterior

columns—and that pain requires the integrity of many small fibres—an arrangement which appears to exist in the antero-lateral region.

General Discussion

Probably owing to the dominance of the sense of sight, we lack an adequate vocabulary to describe our cutaneous sensations. For example, we tend to lump together under the generic heading of "touch" such diverse experiences as result from twitching a hair, dragging a wisp of cotton-wool across the skin, touching the skin with a testing thread, pressing it with a metal rod, or stroking it with the fingers. Conversely, areas of skin are often stigmatized as "analgesic" on the basis of a few prods with a pin. The cutaneous sense is capable of a host of fine discriminations, as any well-compensated blind man readily demonstrates, and this it is the first task of any theory of cutaneous sensation to explain. Such a theory must, of course, account for the gross taxonomical subdivisions of sensory experience, but it must also suggest a mechanism for the fine qualitative distinctions which can be made within each category, and explain the existence of many sensations which appear to bear little introspective relationship to each other.

This problem has always been less than adequately faced by the von Frey theory. von Frey postulated four basic "modalities" of sensation, each with its own anatomically separate neural mechanisms. Gradations in intensity within a given modality could be explained by alterations in the number of impulses per unit time reaching the central nervous system along the specific nerve fibres, but it was not so easy to explain alterations in quality. Again, there seems to be no *a priori* reason to deny the status of "modality" to sensations such as itch, tickle, "heat," and the various subdivisions of painful experience. Attempts were made to account for these as a result of stimulation of different permutations and combinations of the four basic sensory end-organs (Boring, 1942), along the lines of the trichromatic theory of colour vision. The best known of these attempts was that of Alrutz (1900) to explain the sensation of "heat." Work of this kind has never been regarded as completely convincing, and Alrutz has been severely criticised (Jenkins, 1938*a*, 1938*b*).

Conversely, it has always puzzled many that "warm" and "cold," which are in physics only relative terms, should be supposed to possess their own specific end-organs in the body. As Riley (1894) put it: "It is not at all natural to suppose that absolutely different apparatus, distinct and separate, each occupying a local position of its own, would

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be required for these two sensations which are developed by the same form of energy in different quantities."

The second primary problem which confronts any theory of cutaneous sensation is that of sensory dissociation, and here the von Frey theory is more satisfactory. Sensory dissociation—a total or partial loss of some forms of sensation while others are completely or relatively preserved—is a feature of many diseases or injuries of the nervous system. The results recorded in a given case may be a function of the part of the body affected, the stimuli, the testing conditions, and the individual patient, and it may be that in some instances "dissociations" are artefacts, for we cannot as yet compare the absolute energies of qualitatively different stimuli, or the effects of differing skin thresholds. Yet the phenomenon can be a real one, and it follows that there must be some sort of difference between the mechanisms subserving different sensations. The anatomically distinct fibres and pathways of von Frey are well adapted to respond differentially to anatomical lesions or pathological stresses. Nevertheless, one may legitimately enquire what can be dissociated from what, and here we run against some difficulties. Clinically it is rare to find pain dissociated from temperature, and it is almost unknown to encounter abolition of one modality without a very considerable interference with one or more others. Yet we can dissociate experimentally one type of pain from another, though pain is supposedly a basic modality with but one sensory apparatus. If we enquire further, we find that it has been necessary to erect a very considerable superstructure of unverified supposition upon the original theory—the pain fibres must grow faster and further than the touch fibres, they must flock together in the spinal cord but remain separate in the peripheral nerves, and so on.

The specific fibre theory was, and is, no more than a working hypothesis which has never received objective proof. It has not yet been shown that stimulation of a single nerve fibre can ever lead to the experience of a sensation, or that it is even possible for a physiological stimulus to activate one fibre in isolation. In animals it appears that even minimal stimuli arouse several distinct fibres, and the innervation of human skin is such as to suggest that this must be so in man also. We can detect no qualitative difference between the electrical impulses travelling up different nerve fibres in response to different stimuli. Yet it is supposed that the brain distinguishes one sort of stimulation from another by the fact that impulses arrive along fibres which are in some way recognizable. In default of a better explanation we say that the central connexions made by specific fibres differ from each other, but

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the evidence in favour of this supposition is much less than satisfactory.

The facts disclosed by histology run counter to the idea of the morphological differentiation of specific endings, and the physiology of undifferentiated endings appears adequate to subserve most sensations. The adherents of von Frey have now no anatomical evidence on which to pin their specificity except the varying size of cutaneous nerve fibres. The evidence that the size of the individual fibre determines its sensory function is largely indirect, and most of it is derived from a comparison of nerve blocks in man and in animals, a situation in which the influence of fibre size must be only one factor among many. It is unjustifiable to use reaction times for different sensations as evidence in favour of size-specificity, and direct evidence correlating sensation with fibre size in man is extremely scanty. No one has yet compared the fibre spectra of a range of human cutaneous nerves with the sensory thresholds in their territories.

All this is perhaps not entirely satisfactory, and we must sum up by considering the detailed theory put forward by von Frey to be wrong in regard to its explanation of "specific irritability," and very far from proved in regard to its explanation of "specific energy." More fundamentally, though there is no reason to oppose Muller's explanation of the difference between the senses, we must note that there is no satisfactory experimental evidence to support Volkmann's extension of his ideas to apply within the cutaneous sense.

The tide of recent work (Weddell, 1955*a*) is flowing in favour of the pattern theory. It seems to be established that what leaves the skin as a result of cutaneous stimulation is a complex spatially and temporally dispersed pattern of impulses, and this, or something like it, appears to be what arrives at the sensory cortex of the brain, though the vicissitudes which it undergoes in the spinal cord and ascending pathways have not yet been worked out. It is claimed that the physical characteristics of this pattern are the determining factor in the experience of sensory quality. There are no specific fibres and no specific endings, and hence no anatomical difficulties; the structure of the spinal cord and of the peripheral nerves, which contain fibres of differing size and conduction rates, is well adapted to conduct very varied patterns.

Because a pattern can be continuously variable, the pattern theory accounts better than the specific fibre theory for the range in quality of the sensations which can be aroused from the skin. Extended by certain reasonable assumptions—for example, that sparse innervation or a lack of an adequate proportion of large fibres prevents the recognition of

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"touch patterns"—it appears capable of explaining the phenomena of sensory dissociation. The vexed question of the role of fibre size in dissociation becomes more comprehensible if we accept the pattern hypothesis. The pattern theory is no more capable at present than the specific theory of explaining the association between "local sign" and sensory quality, but so little is as yet known in this direction that we can only wait additional information.

Further evidence will no doubt define the extent and validity of the objections to the pattern theory, and for the moment it is perhaps best to reserve judgment. The purpose of this review will have been served if it has drawn attention to the inconclusive nature of much of the evidence on which one of the basic tenets of neurophysiology is founded, and emphasized the importance of an alternative approach to this evidence.

Yet a further word must be added. There is a great need for standardization of stimuli and definition of terms in sensory neurology and neurophysiology. The only practicable way of defining a sensation for clinical or research purposes is to define the circumstances which elicit it, and so diverse are the methods used at present that it is no great exaggeration to say that no two workers mean exactly the same thing by "touch" or "pain." Again, it has not been generally realized that the measure of the intensity of a stimulus should be taken from the threshold intensity and not from any absolute standard. This is particularly evident in relation to thermal stimuli, where a slight change in the skin temperature may lead to a constant stimulus being perceived as warm, neutral, or cold. The same principle applies to other forms of stimulation; it is meaningless to attempt to compare the extinction and recovery of different sensory modalities during a nerve block unless the thresholds of each modality are tested beforehand.

Failure on the part of the clinician or sensory physiologist to realize the contribution he makes by his own testing methods to the result recorded in his notebook has led to considerable confusion. It is a failure similar to that of the physicists, who, until recently, have been observing events within the atom unconscious of the fact that their own presence as observers was a major factor affecting these events. There is no doubt that agreement on standard testing methods would at least reduce the number of obvious discrepancies between the results of different workers when dealing with such problems as the dissociation of sensibility.

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CUTANEOUS NERVES IN LEPROSY
THE RELATIONSHIP BETWEEN HISTOPATHOLOGY AND CUTANEOUS SENSIBILITY[1]

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Introduction

THE purpose of this investigation is to correlate alterations in cutaneous sensibility with the change in pattern of innervation of skin resulting from infection with *Mycobacterium lepræ*.

Fite (1943) and Dharmendra (1952) have already reviewed in detail the literature on the histopathology of nerves in leprosy so that it is only necessary to summarize the position briefly. Danielson and Boeck (1848) published the first systematic study of the morbid anatomy of the disease; they described cellular infiltration of the sheaths and fibres of small and large peripheral nerves. They assumed that the degeneration of the nerve fibres was due to pressure atrophy caused by the inflammatory exudate. Virchow (1882) among others, believed the primary seat of infection in leprosy was in the peripheral nerve itself.

After the identification of the *Mycobacterium lepræ* as the causative agent by Hansen in 1874, Hoggan (1878) was the first to show that mycobacteria could be seen in the numerous cells investing the perineurium and the endoneurium in cases of Leprosy. Cornil and Babes (1885) were the first to observe mycobacteria in the epithelial cells of the hair follicles. Lie (1894) specifically stated that the mycobacteria lay within the myelin sheaths of nerve fibres. Three years earlier, Gerlach, as the result of examining an infected ulnar nerve histologically at different positions along its course, had suggested that the primary seat of infection in "lepra nervosa" was in the skin, the peripheral nerves being affected secondarily by centripetal spread (Dehio, 1897).

[1]Part of this work was presented at the Annual Meeting of the Indian Association of Pathologists, in November 1952, and part of it was presented at the Annual Meeting of the Neurological Society of India, in February 1953.

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That the brunt of the infection is borne by the peripheral or cutaneous nerves in all types of leprosy is accepted by many workers (Woit, 1900; Askanazy, 1912; Muir and Chatterji, 1933; Lowe, 1936; and Pardo-Castello and Piñeyro, 1949). Askanazy was the first to propose that leprosy infects the terminal nerves before involving other structures. Muir and Chatterji (1933) have shown that leprous exudate in the skin is found predominantly in relation to intradermal nerve twigs, becoming heavier as it tracks downwards to reach the subcutaneous nerves.

Saijo and Takino (1929) noted that Meissner's corpuscles containing the greatest number of mycobacteria were the most damaged. Specific neuro-histological (silver) techniques have also been employed on occasions. For instance, Tossujew (1940) observed thickening, fragmentation and varicosity of the nerve fibres in leprous granulomata, and a decrease in the number of nerve twigs in atrophied leprous skin. Ermakova (1948) has reported similar changes in the nerve fibres of skin and peripheral nerves obtained at autopsy following death in patients suffering from leprosy. She stated that concurrent staining for acid-fast bacilli revealed some organisms in the nerve-fibres.

Recent studies by Khanolkar (1951) have also emphasized that changes in or around cutaneous nerve fibres are the basic lesions in leprosy. As Fite (1951) has so effectively summed up, "To the histopathologist all leprosy is neural leprosy . . . The cutaneous nerves related to the skin lesions are involved in all types of leprosy."

The work of Woollard, Weddell and Harpman (1940) and Weddell (1941) suggested that informative histological pictures of intradermal nerves might be obtained in skin infected by leprosy by staining them *in vivo* with methylene-blue and examining them subsequently in whole mounts of skin. A modified technique of this kind was therefore used in this investigation.

Material

232 patients (224 male, 8 female) selected from those attending the out-patient clinic at the Acworth Leprosy Home, Bombay, were used in this study. Their ages ranged from 8 to 67 years and the history of the disease from three months to eighteen years.

The selected patients were divided into two major groups, Neural and Lepromatous, on the basis of a routine clinical examination coupled with :

(1) An examination of the sensory acuity of the affected skin compared with that in the same region on the opposite side of the body.

(2) The number of *Mycobacteria lepræ* detected in smears from the lesions.

(3) The results of the lepromin test.

The terms "neural" and "lepromatous" were adopted from the classification laid down at the International Congress of Leprosy at Cairo, in 1938, and which was in vogue at the time this work was carried out (1951–52). It has not been re-grouped according to the new (only slightly modified) classification laid down at the 1953 International Congress of Leprosy at Madrid. The essentially clinical grouping and subgrouping employed here is based on the distinguishing features outlined below.

The Neural Group consisted of 69 patients. They all had zones of skin in which sensation was either lost or considerably impaired; their lepromin test was invariably positive but either no, or very few, acid-fast bacilli were seen in smears made from the lesions. The neural group were further divided into three fairly distinct subgroups:

(*a*) The macular subgroup; these consisted of comparatively early lesions which took the form of well-demarcated flat areas of hypo-pigmented skin.

(*b*) The tuberculoid subgroup; these consisted of raised or thickened areas of skin, which were either soft and erythematous or firm and pale; resolution at the centre of the lesion frequently accompanied its peripheral extension.

(*c*) The acroteric subgroup; these consisted of relatively large areas of anæsthetic skin of normal appearance resulting from leprous peripheral neuritis of the lateral popliteal and/or the ulnar nerves.

The Lepromatous Group consisted of 87 patients. They all had zones of affected skin in which sensation was either normal or slighly impaired; their lepromin test was negative and a large number of acid-fast bacilli were seen in smears made from the lesions. The lepromatous group were further divided into two fairly distinct subgroups:

(*a*) The macular subgroup; these consisted of comparatively early lesions which took the form of ill-defined flat copper-coloured or hypo-pigmented areas of skin;

(*b*) The diffuse infiltrative subgroup; these consisted of large areas of normal-coloured wrinkled or thickened skin, occasionally with a shiny appearance.

Most of the biopsies in both major groups were taken from the macular type of lesion.

Seventy-six control biopsies were obtained from the patients, the largest number coming from the neural group. The great majority of

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these specimens were secured from apparently normal areas of skin, but 12 biopsies were taken from non-leprous hypopigmented lesions, such as those of pityriasis and vitiligo.

Methods

(1) *Neurohistology.*—The area of skin from which the biopsy was to be removed was injected subcutaneously with 2 per cent procaine hydrochloride. This was followed in 207 cases by an intradermal and subcutaneous injection of 0·02 per cent methylene-blue (Merck) in normal saline. After 20 to 30 minutes, the treated skin (about 2 × 1 cm.) was removed by using a sharp knife moving tangentially to the surface so as to include no subcutaneous tissue. The inner surface of the excised skin was then exposed to air for fifteen to twenty minutes after which it was placed in chilled 8 per cent ammonium molybdate where it remained for twenty-four hours. After this, the specimen was washed in running water for about an hour. The epidermis was then scraped off, the skin dehydrated in chilled redistilled absolute alcohol, cleared in xylol and mounted in balsam for examination as a whole preparation.

In 16 cases hyaluronidase was mixed with the methylene-blue before injection in the hope that this might lead to better diffusion or penetration of the dye, particularly in cases in which considerable exudative or fibrotic changes were suspected. Between 0·25 and 0·35 mg. of hyaluronidase powder (Evans) was dissolved in 25 c.c. of the dye and between 2 and 4 c.c. of this solution was injected into the skin. The presence of the enzyme did not, however, appear to affect the results appreciably. This might have been due either to the small quantity of hyaluronidase used or due to the mixing of the enzyme with the dye before injection (cf. Weddell and Pallie, 1954).

In 25 cases the skin was stained supra-vitally. In these cases the skin was removed immediately after anæsthetization and its undersurface was at once moistened with a few drops of 0·02 per cent methylene-blue in normal saline solution. Fresh drops of dye solution were added every few minutes and the tissue was exposed to the air continuously. When the staining was judged to be optimal, the specimen was transferred to chilled ammonium molybdate and subsequently processed as described above. The time taken for optimal staining was 20 to 30 minutes and at this time the skin appeared to be faint blue in colour. This method had been found by trial to be far superior to the immersion method usually practised, presumably owing to better oxygenation. In view of the statements of Weddell and Zander (1950) concerning the ease with which artefacts can be produced in nerve fibres by rough handling

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of tissues during preparation for microscopical examination, care was taken that all specimens were handled as gently as possible throughout this investigation.

In 17 cases, a small portion of the skin which had been removed was fixed in Zenker's fluid and after embedding in paraffin, 5 μ sections were cut and stained, by Masson's Trichrome for cells and connective tissue, by Mallory's Aniline blue for nerve fibres and connective tissue and by Fite's Carbol fuchsin for acid-fast bacilli.

(2) *Sensory tests.*—All the tests were carried out after covering the subject's eyes.

(*a*) Tactile sensibility was assessed from the reports evoked by brushing the skin with wisps of cotton-wool. At the same time the subject's ability to localize the stimulus was tested by asking him to indicate the site of stimulation.

(*b*) Warmth sensibility was assessed from the reports evoked by contact with a test tube filled with water above 45° C.

(*c*) Pain was assessed from the reports evoked by pricking the skin with a pin: the subject specifically was asked whether he felt pain or contact when stimulated by this means.

Observations

These fall into two interdependent parts, histological and physiological (i.e. comparative changes in sensory acuity). They are reported under four headings:

(1) The overall neurohistological picture as seen under the low power of the microscope. This was used to give a rough guide as to the number of nerve fibres destroyed by the disease.

(2) The overall physiological picture (changes in sensory acuity). This was used to assess both the type and degree of the sensory changes which occurred.

(3) The correlation between (1) and (2).

(4) Specific changes in the pattern of cutaneous innervation and in the morphology of individual nerve fibres and endings. This was used to determine whether the disease affects some particular type of neural organization or nerve fibre more than another.

(1) *The overall neurohistological picture.*—It is not possible to give accurate figures which relate to the number of nerve fibres innervating a given piece of skin. This is chiefly for the reason that skin is innervated by nerve fibres which approach the surface through a cutaneous plexus in which they divide and subdivide repeatedly before terminating (Weddell, 1945). It is possible, however, to grade the density of nerve

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fibres as seen through a low-power objective under the microscope and to express it by a symbol. The symbols chosen in this investigation were (+), (±) and (−). The symbol (+) refers to the presence of cutaneous plexus containing a large number of nerve fibres, as well as isolated nerves ending in relation to hair follicles, in all microscopical fields. This is the picture seen in most "well-stained" control specimens of skin. The symbol (±) refers to the presence of a recognizable cutaneous nerve plexus as well as a few nerves ending in relation to hair follicles in at least three different microscopical fields. The symbol (−) refers to the absence of intact nerve fibres and nerve endings but admits the presence of isolated fragments of degenerating nerve.

The density of innervation in the vitally stained specimens proved to be somewhat more even than in the supravitally stained specimens. However, this was not serious enough for these specimens to be dealt with under a separate heading. The density of innervation in specimens from normal skin and in skin from neural and lepromatous lesions is set out in Tables I and II.

TABLE I.—SHOWING DENSITY OF INNERVATION IN SPECIMENS OF CONTROL ("NORMAL") SKIN AND IN SPECIMENS OF SKIN FROM NEURAL AND LEPROMATOUS LESIONS

Type of specimen	*Control*	*Neural*	*Lepromatous*
No of biopsies	76	69	87
No. showing nerves (Density + and ± taken together)	66	25	55

TABLE II.—DETAILED ANALYSIS OF DENSITY OF INNERVATION

	Control			*Neural*			*Lepromatous*	
	Neural	*Lepro-matous*	*Non-leprous Hypo-pigmented*	*Macu-lar*	*Tuber-culoid*	*Acro-teric*	*Macular*	*Diffuse infil-trative*
Total biopsies	60	16	12	48	14	7	78	9
Density (+)	50	5	8	6	1	0	13	1
Density (±)	8	3	1	16	1	1	38	3
Density (−)	2	8	3	26	12	6	27	5

Table I shows that significantly more normal nerve fibres and endings are seen in the control group than in either the lepromatous or the neural groups. Moreover it also shows that in the specimens examined the number of normal nerves and endings seen in the lepromatous group is greater than in the neural group.

A number of interesting points emerge from Table II.

Neural group: The macular subgroup, which are early lesions, contained nerve fibres in about half (22 out of 48) of the cases examined. The tuberculoid subgroup, which are usually older lesions, contained nerve fibres in a much smaller proportion (2 out of 14) of cases. In only one of the acroteric cases were a few normal nerve-fibres seen.

Lepromatous group: The macular subgroup, which are again early lesions, contained nerves in about two-thirds (51 out of 78) of the specimens examined. In the diffuse infiltrative lesions, on the other hand, rather less than half (4 out of 9) of the specimens contained nerve fibres.

Thus, in the macular subgroups (both neural and lepromatous) which consisted of soft flat early lesions, more nerve fibres can be seen than in subgroups representing later stages in the disease process. Nevertheless, fewer nerve fibres are seen in the other subgroups comprising the neural group than in those comprising the lepromatous group.

(2) *Physiological observations (sensory tests).*—The sensory acuity of each area of skin was tested before removal. The results of these tests are also difficult to express quantitatively. As in the case of the histological observations, it was found most convenient to express them in the form of graded symbols. The symbol (+) has been used to indicate "normal" sensory acuity, i.e. similar to that reported when the control area on the opposite side of the body was stimulated. The symbol (±) indicates impairment of sensibility; in the case of warmth and pain, impairment was synonymous with a raised threshold; in the case of touch, it included cases in which subjective changes in tactile sensibility were reported by the patient from which it was possible to infer a diminution of tactile acuity, as well as impairment of tactile localization. Pricking of the skin with a pin in cases in which pain sensibility was lost either evoked no report at all or a report of touch. The results of the sensory tests are set out in Table III.

In the contralateral control areas, reports relative to all sensations were taken to be "normal" and it is in relation to these reports that the above table was constructed.

In the first place it can be seen that, in both of the two main groups of cases with minimal sensory loss, touch acuity was apparently unimpaired. In cases in which the sensory loss was greater, touch acuity was always less affected than either warmth or pain sensibility. With one exception (a lepromatous macule), warmth and pain sensibility were never reported as being felt when touch was not reported.

From Table III it can be seen that, of the 69 neural cases examined, cutaneous sensibility was affected in 66. Sensations of touch, warmth

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TABLE III.—DETAILED ANALYSIS OF ACUITY OF TACTILE, THERMAL AND PAIN SENSATIONS IN THE TWO MAIN GROUPS OF CASES

		Neural group (69)				*Lepromatous group* (87)		
Sensibility	*Degree of acuity*	*Macular*	*Tuberculoid*	*Acroteric*	*Total*	*Macular*	*Diffuse infiltrative*	*Total*
Touch, warmth and pain together	(+)	2	1	0	3	36	6	42
	(±)	17	4	3	41	5	1	6
	(−)	7	6	4		0	0	
Touch	(+)	24	4	0	28	72	8	80
	(±)	9	1	0	41	6	1	7
	(−)	15	9	7		0	0	
Warmth	(+)	2	1	0	3	44	6	50
	(±)	19	3	1	66	25	3	37
	(−)	27	10	6		9	0	
Pain	(+)	2	1	0	3	41	7	48
	(±)	36	7	3	66	34	2	39
	(−)	10	6	4		1	0	
Hyperalgesia		0	0	0		2	0	

and pain together were impaired or lost in 41 of these. In the remaining 25 cases, touch was preserved whilst warmth and pain were impaired. By contrast, of the 87 lepromatous cases examined, cutaneous sensibility was disordered in 45. Sensations of touch, warmth and pain together were affected in only 6 of these. In the remaining 39 cases touch was preserved (with one exception) whilst warmth and/or pain were affected, 2 of these manifesting hyperalgesia. Sensory acuity was apparently unimpaired in 42 cases.

From this it is clear that, although sensory impairment occurs more often and to a greater extent in the neural group, there is nevertheless an appreciable diminution in the sensory acuity for both warmth and pain in the lepromatous group.

The general pattern of sensory loss was the same in both the main groups of cases. Warmth and pain were both affected to a greater extent than touch and usually affected together. In all the neural and most of the lepromatous cases loss of warmth sensibility went hand in hand with loss of pain sensibility; in only 6 of the lepromatous cases could pain be evoked to the exclusion of warmth and in 6 warmth to the exclusion of pain.

From Table III it is clear that lepromatous lesions are least affected from the point of view of loss of sensory acuity. However, both the

macular and diffuse infiltrative subgroups are affected to the same extent. Among the Neural Group the least affected is the macular subgroup, the most affected the acroteric subgroup, whilst in tuberculoid lesions loss of sensory acuity lies between these two extremes. It is of interest that in two cases with lepromatous macular lesions hyperalgesia was encountered; this took the form of a lowered threshold and an exaggerated reflex response to light pin-prick.

(3) *Correlation of Histological Observations with Results of Sensory Testing.*—Detailed analysis in individual cases has been given elsewhere (Dastur, 1953). Notes on a few selected cases are presented in the legends to the illustrations in this paper.

TABLE IV.—SHOWING CORRELATION BETWEEN NEUROHISTOLOGICAL AND SENSORY FINDINGS IN THE TWO MAIN GROUPS

NEURAL GROUP

Physiology		*Neurohistology*		
		Normal	*Diminished*	*Absent*
Acuity		(+)	±	(−)
1. Normal	3	2	0	1
2. Pain and warmth impaired or lost	25	5	13	7
3. Touch, warmth and pain impaired or lost ...	41	0	5	36
Total	69	7	18	44

LEPROMATOUS GROUP

Physiology		*Neurohistology*		
		Normal	*Diminished*	*Absent*
Acuity		(+)	(±)	(−)
1. Normal	42	9	22	11
2. Pain and/or warmth impaired or lost	39	5	16	18
3. Touch, warmth and pain impaired or lost ...	6	0	2	4
Total	87	14	40	33

The data relevant to this paper are set out in Table IV. From this it can be seen that of the 42 lepromatous lesions in which the sensory acuity was apparently normal, only 9 showed an abundance of nerve fibres and endings in all fields under the low power of the microscope. In 22 cases, however, at least some normal nerve fibres and endings were seen. In 11 cases no normal nerve fibres were seen. Of the 76 "normal" control specimens of skin (Table II) on the other hand, 55 showed an abundance of nerve fibres and endings in all fields under the low power of the microscope. 11 showed a few normal nerve fibres and endings, and in 10 no normal nerve fibres were seen. More-

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over, in the skin taken from non-leprous hypopigmented areas (fungus infections such as pityriasis) in which sensory acuity was normal, 8 of the 12 specimens revealed many normal nerves and endings and one a few normal nerves and endings. 3 showed no nerves or endings. Thus, in the case of a lepromatous lesion exhibiting no loss of sensory acuity there is a greater chance of finding a reduction in the density of innervation as compared to that seen in any of the control areas of skin.

This is even more convincingly demonstrated if the "normal" control biopsies are analysed. Of the 60 biopsies from the neural cases (Table II), 50 showed an abundance of nerves whilst of the 16 biopsies from the lepromatous cases only 5 showed an abundance of nerves.

This apparent lack of correlation between the results of sensory testing and neurohistological observations can only mean one of two things;

(1) that a number of nerve fibres in the skin remain unstained because they are enveloped either by the mycobacteria, their products of metabolism or the cellular infiltrates which arise;

(2) that small changes in sensory acuity are not recognized because of the particular clinical methods used to evoke reports of sensations.

Since both degenerating and regenerating nerve filaments enmeshed in inflammatory exudates were often seen, it is unlikely that the neurohistological technique is responsible. On the other hand, the methods of testing for touch, warmth and pain were not particularly exhaustive and the response evoked was naturally subjective rather than strictly comparative. This suggests that in these cases the sensory tests commonly used are not so delicate an index of neural damage as is the examination of histological material.

Apart from this the correlation is good. For instance, of 25 cases in the neural group with impairment or loss of warmth and pain sensibility, 18 showed the presence of some or a few normal nerve fibres and endings. By contrast, of 39 cases in the lepromatous group, with impairment or loss of warmth and/or pain sensibility, 21 showed the presence of some or a few normal nerve fibres and endings.

An even better correlation emerges in relation to touch sensibility. When touch, warmth and pain sensibility together were impaired or lost, nerves were never found in abundance in either of the two main groups; only 2 out of 6 lepromatous lesions and 5 out of 41 neural lesions revealed a few normal nerve fibres. This clearly indicates that loss of warmth and pain sensibility occur when only a few nerve fibres are affected, whereas touch is lost only when a larger number of nerve fibres are affected.

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(4) *Detailed neurohistological observations.*—Figs. 1 and 2 show the pattern of innervation which is similar to that seen in vitally stained whole mounts of normal human skin. Fig. 1 shows the cutaneous plexus and fig. 2 shows nerves clustering around a hair forming the so-called "tricho-neural apparatus." The general pattern was similar in biopsies from non-leprous areas of hypopigmentation.

Encapsulated nerve endings were not seen in any of these 232 specimens of hairy skin, although artefacts stimulating them have occasionally been encountered (fig. 3). On rare occasions the shape and disposition of a hair follicle was so distorted by the disease process that it took on the appearance of a tangled skein of axons and so came to resemble a nerve ending. However, in all but one instance, the remnants of a hair lying among the follicular cells could be seen. The nerves leaving the cutaneous plexus always appeared to end freely. The fine terminal filaments ending in relation to the dermal tissues and blood vessels resembled those seen in the cornea (Weddell and Zander, 1950). Those ending in relation to hairs were similar but more circumscribed (fig. 4).

Examination of the methylene-blue stained preparations under higher magnification showed that the axis cylinders of nerve fibres of the cutaneous plexus were smooth and continuous but they varied in thickness when they were traced for some distance. A few axis-cylinders (usually the finer ones) were beaded and some even consisted of rows of discontinuous beads (fig. 1). In this they resembled the beaded fibres seen in the cornea and are not necessarily representative of pathological changes. Formalin and osmic acid are well known to cause nerve fibres to assume a "nodose" appearance and it is probable that the alcohol (used for tissue fixation) does the same thing in the case of methylene-blue stained preparations. Furthermore, the delicacy and instability of the terminal ramifications of peripheral nerves is well recognized (e.g. Weddell and Zander, 1951, and Nageotte, 1932), and continuous degenerative and regenerative changes are said to be occurring among these fibres. In some specimens the Schwann elements (sheaths and nuclei) were stained. This is also probably an artefact for they were more apparent in preparations in which there were many nerves ("normal" and lepromatous areas—Table V).

Figs. 5 to 8 are samples showing increasing degrees of neural disorganization in leprosy. The changes seen varied from slight irregularities in the arrangement and density of peri- and inter-follicular nerves, to a complete disappearance of all nerve fibres. Typical degenerative fragmentation of axons (Weddell and Glees, 1941) was

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seen in both neural and lepromatous lesions, mostly in the macules. These fibres were either bare or ensheathed and were sometimes accompanied by normal and/or regenerating fibres.

TABLE V.—PREPARATIONS SHOWING QUALITATIVE CHANGES IN NERVES

Normal skin (76)		*Lepromatous lesions* (87)		*Neural lesions* (69)		
From neural cases	*From lepromatous cases*	*Macular*	*Diffuse infiltrative*	*Macular*	*Tuberculoid*	*Acroteric*
52	7	49	5	25	5	2
59		54		32		

Although the methods themselves were clearly responsible for some of the artefacts (Weddell and Zander, 1950) this alone did not make it impossible to say in the case of any given nerve fibre whether or not it was undergoing pathological changes. The clinical history, sensory findings and overall histological picture were all helpful in deciding the issue. Signs of nerve regeneration are less likely to be confused with artefacts than degenerative changes. In both lepromatous and neural macules, fibres which had all the characteristics of regenerating nerves were seen; some of them being surmounted by growth cones (Weddell, 1942). On rare occasions, a single smooth segment of axon was seen in the region of a hair follicle. It was difficult in such a case to decide whether it was a single remaining normal nerve or a recently regenerated fibre.

In some specimens, irrespective of the clinical group or subgroup in which the case appeared, clusters of inflammatory cell nuclei were observed in close proximity to the neural pathways irrespective of whether they contained fragments of axis-cylinder, regenerating nerve fibres, or consisted solely of Schwann elements (fig. 8). In anæsthetic patches, no nerves were seen and it was significant that in such specimens the cells of the sweat and sebaceous glands as well as smooth-muscle fibres could no longer be identified after methylene blue staining. In addition there were always accumulations of round and irregularly shaped nuclei around the hairs in these specimens. Dendritic cells were also frequently encountered lying close to damaged neural pathways (fig. 7), but in no greater numbers than in normal skin. They resemble the dendritic cells of Billingham (1948, 1949). The chief accumulations of inflammatory cells were orientated around degenerating nerve fragments or in columns in relation to the Schwann elements outlining the position of the cutaneous nerve plexus and the nerve fibres which proceeded from it towards their terminations.

The findings in the 17 specimens stained in Masson's, Mallory's and Fite's stain, respectively, confirmed the observations recorded above. Ten of the specimens were from the lepromatous group, 7 being from the macular and 3 from the diffuse infiltrative subgroups. Seven were from the neural group, all being obtained from lesions in the macular subgroup. The inflammatory exudates in the lepromatous macules were larger and contained more cells than those in the other groups. The cells were of the mononuclear and pre-Virchow type with vacuoles in the cytoplasm. Mature Virchow cells with large vacuoles were only encountered in the diffusely infiltrated lesions. In this group a conspicuous feature was the flattening of the epidermal rete cones and the appearance of a clear subepidermal zone.

In the neural macules the exudate was small, and only found in the more superficial layers of the dermis in close relation to the neural pathways. The cells were mainly large mononuclear histiocytes together with a few lymphocytes and an occasional epithelioid cell.

The nerves in the dermis of the lepromatous macules frequently appeared to be normal though enveloped in a dense inflammatory exudate; sometimes the perineurium was infiltrated with cells, and on occasions the endoneurium appeared to have a hyaline appearance (Khanolkar, 1951). The nerve fibres in the dermis of the neural macules, on the other hand, were usually disorganized by the disease process.

In the vertically cut Mallory-stained sections it was possible to compare the number of nerve twigs per unit area of section. In the seven neural macules there was a total of 61 nerve twigs. These figures compare well with those of Decoud (1948).

Many acid-fast bacilli were seen in every section coming from a lepromatous lesion. They were found lying singly or in clumps either within the reactive cells or elsewhere among the nerve fibres. No acid-fast bacilli were seen in sections from any of the neural macules.

Discussion

Four important points emerge from these observations. The first is that observations based on the examination of over 200 specimens of skin from many different parts of the body allow of the generalization that there are, to all intents and purposes, no encapsulated nerve endings in hairy skin in man. The work of Sinclair, Weddell and Zander (1952) foreshadowed that this state of affairs might obtain.

Two observations suggest that the encapsulated nerve endings found in glabrous skin and exposed mucous membranes are homologous with the "tricho-neural" apparatus. The first is that nerves terminating in

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relation to damaged hair follicles do, in fact, resemble encapsulated nerve endings to some extent. The second is that the sharp distinction formally drawn between perifollicular "nerve baskets" and interfollicular free nerve endings is now known to have been exaggerated. It also follows from these observations that warmth, cold and pain must be subserved by unencapsulated nerve endings as they are in the cornea (Goldscheider and Brückner, 1919; Zander and Weddell, 1951). It therefore seems not unlikely that unencapsulated nerve endings can subserve all the so-called primary modalities of common sensation.

The second point of importance is that under the conditions of these experiments the sensory tests did not suggest any change in sensory acuity until a considerable number of nerve fibres had been destroyed. This is perhaps partly explicable on the basis that the tests were somewhat crude. Nevertheless, the findings are of interest for they also point to the fact that peripheral sensory innervation carries a large "safety factor." In other words, that the normal density of innervation obtaining in hairy skin seems to be well in excess of the minimum required for man to transduce sufficient touch, warmth, cold and pain stimuli to lead a "normal" existence.

The third point of importance is that cutaneous nerve fibres of all sizes and destination are affected in leprosy, the most superficial nerves being affected before those situated more deeply. In this connexion it will be remembered that under the conditions of these experiments warmth and pain were together affected before touch. Light touch is presumably primarily subserved by nerves ending around hairs and these are situated in a deeper plane than most of the other terminals. This reinforces the notion that the superficial unencapsulated nerve endings are associated with warmth, cold and pain (and presumably touch in between hairs). It does not support the concept of a rigid number of specific "modalities" and refutes the widely held belief that specific nerve terminals subserve specific sensory modalities (von Frey, 1895). That the whole is more than the algebraic sum of its anatomical components seems, from the above observations, to hold in the case of cutaneous sensibility. The peripheral analysis of stimuli would appear to be subsidiary to their central interpretation. A sensation thus emerges as a sensory gestält.

The greater and earlier degeneration of the finer sub-epidermal axons, in contrast to the later and lesser involvement of the deeper myelinated peri-follicular nerve fibres, tends, moreover, to substantiate the concept of a centripetal spread of leprous infection (Dehio, 1897; Khanolkar, 1951). It would in turn account for the persistence of

tactile sensibility in the face of an appreciable overall reduction in dermal innervation.

The points of similarity between encapsulated nerve endings and normally innervated hairs is of more than mere histological interest. The rôle of encapsulated nerve endings in tactile localization and discrimination is undisputed (Weddell, 1945). The tricho-neural apparatus, by virtue of its hair, serves not only to extend tactile sensibility a little beyond the surface of the body but it also constitutes a mechanism for accurately localizing light touch throughout the hairy skin. False localization concurrent with an adequate appreciation of contact with a wisp of cotton-wool was observed in a few of the cases and can only be accounted for by a reduction in the density of perifollicular innervation in a given lesion.

The fourth point of importance is that these observations support the notion that there is no such thing as "non-neural" leprosy, either from the sensory or the neurohistological point of view. As already stated in the Introduction, the word neural has been used throughout this paper to conform to an accepted classification only. Microscopical evidence of changes in the quantity and quality of nerve fibres in the cutaneous lesions has been encountered in lepromatous as well as in so-called neural leprosy.

Both degenerating and regenerating nerves have been seen in both case groups and it is of interest that both processes should appear together in time and space. This feature has also been noted in the case of skeletal muscles in leprous polyneuritis (Dastur, 1955). The presence of regenerating nerves suggests a favourable prognosis provided early treatment is successful.

Hyperalgesia is a phenomenon which has been described in many phases of leprosy. Hansen and Looft (1895) have described hyperalgesia as occurring in the early stages of neural leprosy; Cochrane (1947) mentions it as a feature of the reactive stage of tuberculoid leprosy; Muir (1948) states that it occurs in the course of the leproma reaction; whilst Chaussinand (1950) refers to it merely as one of the early clinical findings of the disease. Figueredo (1952) has noted that hyperalgesia occurs only among lepromatous patients. It is thus of interest that in the present series of over 200 cases, only 2 have manifested hyperalgesia and both were young patients with lepromatous leprosy.

In both these cases, prominent cellular exudates were seen enveloping normal, degenerating and a particularly large number of regenerating nerve filaments. These features have been shown to be associated

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with hyperalgesia under certain circumstances (Weddell, Sinclair and Feindel, 1948).

In relation to the specific problem of leprous hypopigmentation, all that can be said from these observations is that there is no direct correlation between the status of intradermal nerve fibres and the presence of dendritic cells, nor between either of these and the lack of cutaneous pigmentation. The latter appears to be the result of a functional rather than a structural aberration of the melanoblasts (Wade, 1934).

Summary

(1) The sensory acuity (touch, warmth and pain) of 232 areas of skin in leprous patients was determined. The neurohistological picture in whole mounts of skin from these areas was then examined after vitally staining with methylene-blue. Both sets of observations were then correlated.

(2) The patients were classified in accordance with the suggestions laid down at the International Congress (Cairo, 1938). 69 "neural," 87 "lepromatous" and 76 "normal" (including non-leprous hypopigmented) areas of skin were examined.

(3) In nearly all the "neural" and more than half the "lepromatous" cases there was loss or impairment of pain and/or warmth sensibility. In two-thirds of the "neural" but only in one-twelfth of "lepromatous" cases, was there concomitant loss or impairment of touch sensibility.

(4) Warmth and pain sensibility were usually affected concurrently and in early lesions, touch only being affected in older and more severe lesions.

(5) The density of innervation was greatest in "normal" skin, rather less dense in skin from "lepromatous" lesions and least dense in skin from "neural" lesions.

(6) Macules (early, soft, hypopigmented lesions) either neural or lepromatous, contained fewer damaged nerve fibres than the other types of lesion.

(7) The correlation between sensory testing and nerve damage was generally good although sensory impairment was not apparent in some "lepromatous" cases which exhibited considerable nerve damage. This suggested a "safety factor" in cutaneous innervation, despite the fact that the sensory testing methods were somewhat crude.

(8) No encapsulated nerve-endings were seen in any of the areas of skin examined. Since they were all taken from "hairy" zones it is

reasonable to assume that such endings do not normally occur in hairy skin in man.

(9) All nerves which could be traced towards their termination apparently ended freely. This applied to those ending in the dermis and in relation to blood vessels as well as those related to hairs, the so-called "tricho-neural apparatus."

(10) These observations indicate that the inter-follicular free nerve endings subserve warmth as well as pain sensibility.

(11) The fact that touch was only affected in the more severe forms of lesion is explained on the basis that the hairs lie in a deeper plane and that the disease spreads centripetally.

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LEGENDS TO PLATES

All figures are photomicrographs or camera-lucida drawings of whole-mounts stained vitally with methylene-blue.

PLATE LVII

FIG. 1.—From a female patient aged 45 with many "neural" macular lesions. Biopsy from a small macule in region of Scapula. *Sensory acuity;* normal. *Neurohistology;* normal density. Some degenerating and regenerating nerves. The drawing shows part of the cutaneous plexus of nerves. There is one axon (marked with an arrow) having the morphological characteristics of a regenerating nerve fibre. 16 mm. objective, × 12 eye-piece.

FIG. 2.—From a male patient aged 24 with a single old-standing tuberculoid lesion. Biopsy from a small flat non-leprous hypopigmented area on anterior surface of arm (probably pityriasis). *Sensory acuity;* normal. *Neurohistology;* normal density of innervation. The photomicrograph shows stem axons converging on a hair follicle. Note the large number of axons arising from different parts of the cutaneous plexus, associated with single hairs in this region of the body. 16 mm. objective, × 12 eye-piece.

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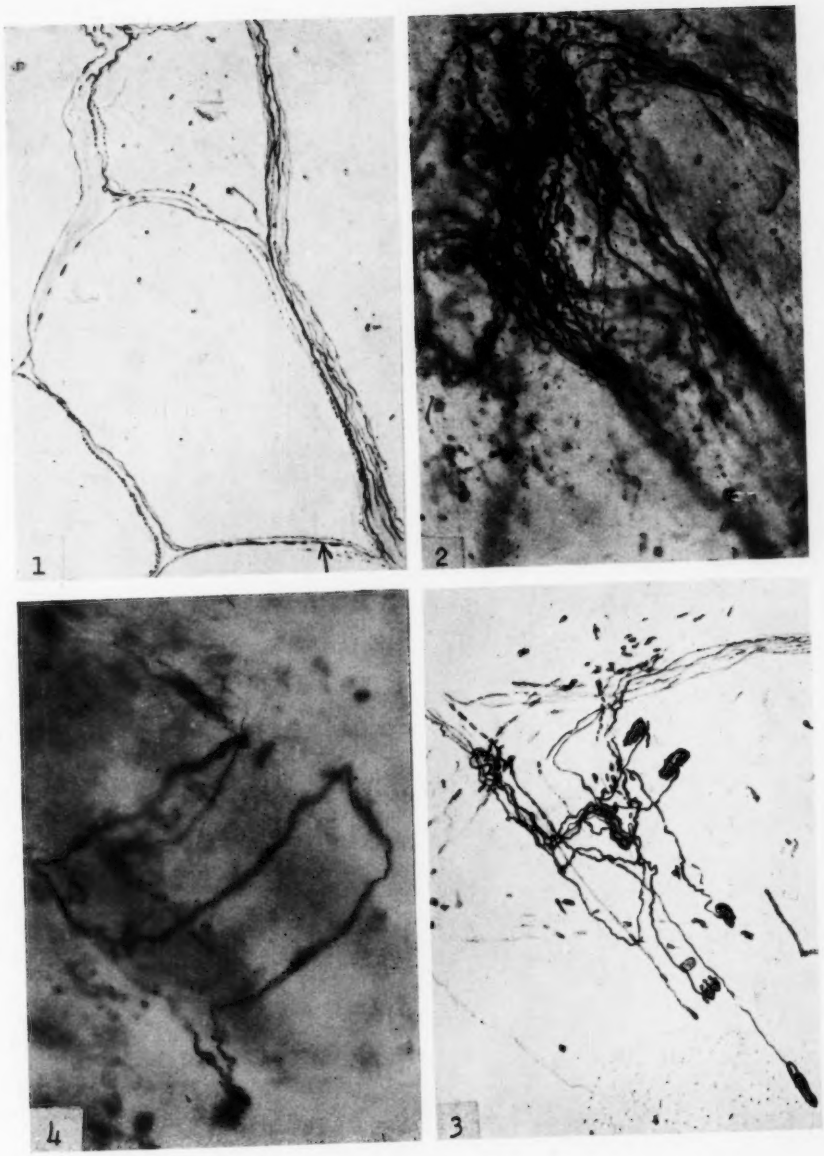
PLATE LVII



To illustrate article by Darab K. Dastur.

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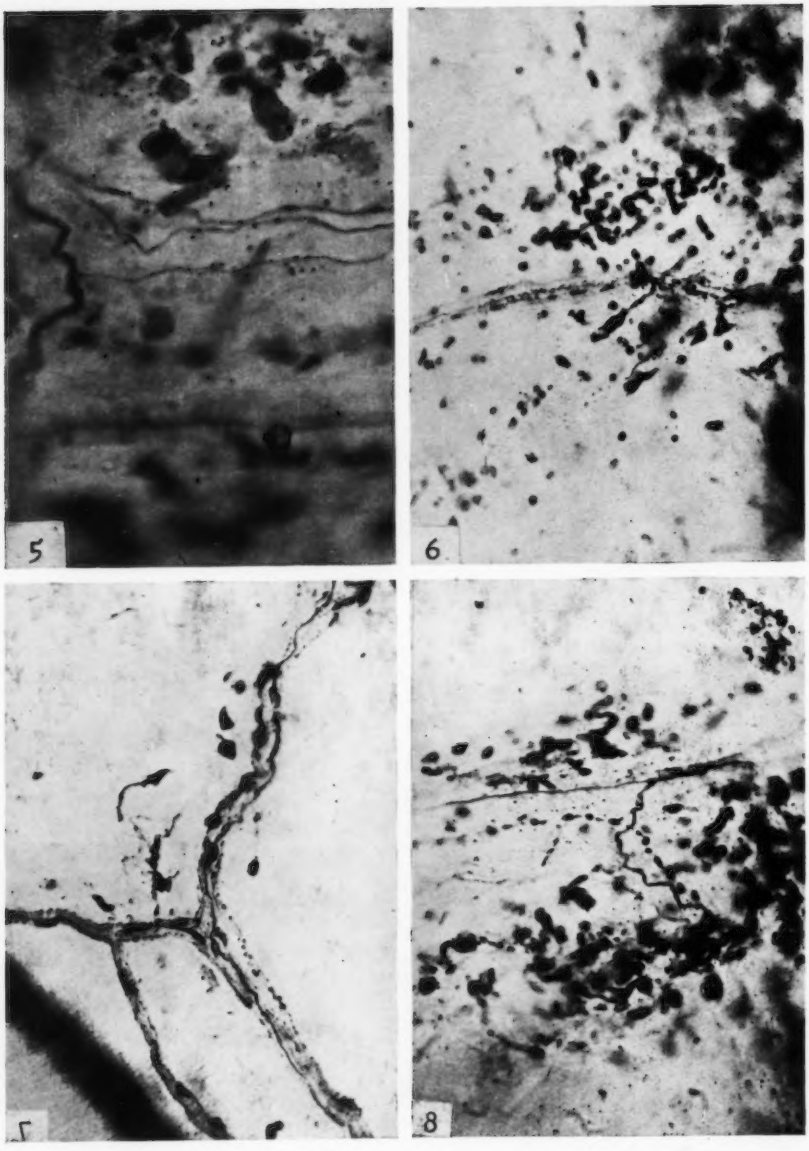
PLATE LVIII



To illustrate article by Darab K. Dastur.

FIG. 3.—From a male patient aged 31 with "neural" macules. Biopsy from healthy-looking skin on lateral surface of arm. *Sensory acuity;* normal. *Neurohistology;* normal density of innervation; preparation "overstained" to some extent. The drawing shows the effect produced when a nerve bundle is stretched and ruptures. The axons spring back and form complicated coils which simulate Krause end-bulbs. No capsular cells can be seen, however. 16 mm. objective, × 12 ocular.

FIG. 4.—From a male patient aged 28 with lepromatous macules, and nodules on both ears. Biopsy from an ill-defined macule on shoulder; *Sensory acuity;* normal. *Neurohistology;* density of innervation reduced to level (±). The photomicrograph shows delicate terminal filaments arising from a single stem axon and terminating freely in relation to the tissues of a hair follicle. 4 mm. objective × 5 ocular.

PLATE LVIII

FIG. 5.—From a male patient aged 19 with thickened lateral popliteal nerves and acroteric lesions on dorsum of feet. Biopsy from a well-defined macule on loin. *Sensory acuity;* touch normal warmth absent, pain absent. *Neurohistology;* reduction in number of axons seen to level (±). The photomicrograph shows normal and regenerating axons lying within an exudate of mononuclear inflammatory cells. There are very few axons in the bundle, the majority having degenerated, the Schwann elements alone remaining. 4 mm. objective, × 5 ocular.

FIG. 6.—From a male patient aged 35 with lepromatous leprosy. Biopsy from centre of slightly hypopigmented area of lepromatous infiltration on anterior surface of arm. (Hyaluronidase injected with dye.) *Sensory acuity;* normal. *Neurohistology;* density of innervation normal. The photomicrograph shows degenerating nerve fibres lying in an exudate of lymphocytes and histiocytes. One axis cylinder is still intact in this position but when traced distally it was seen to be fragmented. Towards the termination of the bundle only a faint sheath, with fusiform nuclei, and fragments of axis cylinder remained. 16 mm. objective, × 12 ocular.

FIG. 7.—From a male patient aged 38 with lepromatous leprosy. Biopsy from macule situated below right costal margin. *Sensory acuity;* touch normal, warmth normal, pain diminished to (±). *Neurohistology;* normal density of innervation. The photomicrograph shows part of the cutaneous nerve plexus which is "overstained." The long smooth axon running vertically through the entire field is a stem fibre which is giving rise to extremely fine sprouts surmounted by growth cones at intervals along its course. This is an example of collateral nerve regeneration. Dendritic cells are stained in this specimen. 16 mm. objective, × 12 ocular.

FIG. 8.—From a male patient aged 19 with thickened lateral popliteal nerves and acroteric lesions on dorsum of feet. Biopsy from well-defined macule on loin. *Sensory acuity;* touch normal, warmth absent, pain absent. *Neurohistology;* density of innervation reduced to level (±). The photomicrograph shows normal and degenerating axons surrounded by a mononuclear cell exudate in the region of an infected hair follicle. 16 mm. objective, × 12 ocular.

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OBSERVATIONS ON CHEMICAL AND NEURAL MECHANISMS OF CUTANEOUS HYPERALGESIA, FLARE AND INFLAMMATION

PART I BY J. A. HARPMAN
PART II BY J. A. HARPMAN AND T. P. WHITEHEAD

(From the Departments of Ear, Nose and Throat Surgery and Biochemistry Warwick Hospital, Warwick)

Definition of cutaneous hyperalgesia.—In the observations recorded in this paper, skin was considered to be hyperalgesic when slight pressure, tension or friction to it aroused pain. Pain was sometimes perceived spontaneously in such an area.

PART I

The Problems Investigated

Lewis (1936, 1937*a*, 1942) has described how in human subjects minute skin injuries become surrounded by areas of cutaneous hyperalgesia. These hyperalgesic areas may be of relatively large size, they take a little while to develop, they have certain relations to subcutaneous veins, and the production or spread of the areas of hyperalgesia can be influenced in a variety of ways by intra- and sub-epidermal injections of a local anæsthetic solution and by altering the state of the local circulation. This work was done, using such relatively simple methods of investigation as were available to me, with a view to answering the following questions:

(1) Which set of peripheral nerve fibres and endings is concerned in the production of skin hyperalgesia following small skin injuries?

(2) Why are areas of cutaneous hyperalgesia sometimes more severe over and delimited by superficial veins and why do these areas often extend along superficial veins?

(3) How do skin injuries only a few millimetres square produce areas of hyperalgesia often many centimetres square?

These studies then led to investigation of some aspects of inflam-

mation and flare, and to more chemical investigations on skin hyperalgesia, reported and discussed in Part II of this paper.

Material and Methods

Observations were made:

(1) on the forearms and anterior abdominal walls of two normal human subjects,

(2) on the forearms of a third normal human subject,

(3) on the left forearm of two patients in whom the left inferior cervical and first, second and third thoracic sympathetic ganglia had been removed about a month previously,

(4) on the foreheads and faces of two patients in whom the whole trigeminal sensory nerve root on one side had been divided by the posterior fossa approach some three and six months previously, and of two normal subjects, and on the foreheads of patients in whom the supraorbital and supratrochlear nerves had been divided on one side during frontal sinus operations,

(5) on the thoracic and upper abdominal walls of patients in whom the intercostal nerves on one side had been locally anæsthetized for surgery, and on the anterior aspect of the neck of patients in whom the cervical nerves on one side had been divided during surgical operations.

One of the normal subjects was a medical man; the others were lay persons. The forearms were supported horizontally except when otherwise stated. Each of the observations reported in this paper was made at least twice, and usually up to six times, and mostly on two subjects, but the unpleasantness, indeed the painfulness, of many of the experiments rendered it difficult to perform them more often or to obtain more subjects on whom to perform them. The total number of experiments on which these observations are based is about 80. It is appreciated that a more quantitative treatment of this work would be advisable, but this would have required a much greater number of experiments than that to which the subjects felt able to submit.

Areas of cutaneous hyperalgesia were produced by injecting intraepidermally about 1/10 of a minim of alcohol, benzene or chloroform with a tuberculin needle and syringe, or by injuring areas of skin about 2 × 4 mm. square by crushing with fine forceps, burning, or freezing with carbon dioxide snow.

In 6 experiments on two subjects either the lateral or the medial cutaneous nerve of the left forearm was anæsthetized by infiltration, around the nerve, of 2 to 4 c.c. of 1 per cent to 4 per cent procaine

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solution in normal saline, the nerve first being located just below the elbow by faradic stimulation. Hyperalgesic areas of skin were produced in these forearms and the effects of these nerve blocks on the hyperalgesia determined. The effects of injecting solutions of procaine intra- and sub-epidermally in and around sites of small skin injuries on the hyperalgesia produced by trauma were also studied.

On the forearm of one subject observations were also made on the sensory phenomena occurring around 7 skin ulcers, extending into the superficial layers of the dermis, produced by the intra- and sub-epidermal injection of benzene in quantities of up to half a minim.

Cutaneous sensations were tested for as follows:

pain: by the introduction of fine steel needles into the skin,
touch: with a set of von Frey hairs and a fine camel-hair brush and by bending the hairs of the skin whenever present,
cold and warmth: by applying to the skin cooled or warmed copper rods 1 mm. in diameter.

Hyperalgesia was considered to be present when pain was aroused by slight pressure to the skin with a blunt instrument, or rubbing it lightly with a finger, or gently picking up a fold of it between a finger and thumb. The subjects were blindfolded during tests.

It was found that, if 1 to 7 minims of 1 in 20,000 or 1 in 1,000 adrenalin solution be injected intra-epidermally with a fine tuberculin needle and syringe, there results an area of blanching that, by its spread, indicates the diffusion of the solution through tissue spaces and lymphatics, the contrast between blanched and unblanched skin being enhanced by warming the part so as to produce cutaneous vasodilatation in normal skin. Observations were made on such spread in the forearm, anterior abdominal wall and forehead. There were investigated the effects, on this spread and on skin hyperalgesia, of occluding the arterial and venous circulations to the limb; a sphygmomanometer was employed for this and also a special clamp tourniquet with which it is possible to occlude the main artery to a limb while causing little interference with its venous return.

The effects of injecting $\frac{1}{2}$ to 2 minims of 1/1000 adrenalin hydrochloride in water solution, 1 to 5 minims of aqueous solutions containing 1/300–1/100 grain atropine sulphate or 0·03–0·1 gramme acetylcholine sub- or intra-epidermally into hyperalgesic skin was determined, as were also the effects on such skin of immersion in water at temperatures such as to produce cutaneous redness or pallor.

Observations

Some features of the hyperalgesia and flare.—Skin injuries such as those mentioned above gradually became surrounded, in from 20 seconds to several hours—usually a few minutes—after being inflicted, by local reddening, whealing, flare, sometimes slight swelling and an area of hyperalgesia several centimetres square. These areas were sometimes as large as a 11 × 15 cm. In the forearm they were generally so disposed that the longer axis of the area was parallel to that of the limb; in the abdomen, the longer axis was transverse.

The extent of the hyperalgesic area and the severity and speed of development of the hyperalgesia varied in the same subject, in the same part, and from similar injuries, at different times.

The hyperalgesia and the occasional slight swelling were more severe at and near the site of the causative trauma than in the periphery of the hyperalgesic area. When, on either the extensor or the flexor aspect of the forearm, an area of hyperalgesia was large, its longest radius from the site of injury ran distally when the lesion was near the elbow, and proximally when it was near the wrist.

The areas of hyperalgesia and flare resulting from the same injury often developed at different rates; when both areas were fully developed, there was often close correspondence between their borders.

Hyperalgesic skin was found to be hypoæsthetic. When an area of skin, either some hours or even some days after a small injury, ceased to be hyperalgesic, it often itched, sometimes for several days; itching was sometimes the sole sensory abnormality occurring in and around skin the site of a small injury.

Sympathectomy and the hyperalgesia.—Similar reactions to skin trauma were found to occur in the left forearms of the two subjects in whom the left upper limb had undergone sympathetic denervation.

Hyperalgesia, flare and the mid-line.—In the anterior abdominal wall, skin injuries such as described above placed 8 to 10 mm. from the mid-line produced areas of hyperalgesia and flare involving skin on both sides of the mid-line. The spread described was prevented by sub- and intra-epidermal infiltration with procaine solution along the mid-line. The hyperalgesia and flare often extended for about 1½ in. on the uninjured side (fig. 4, page 638).

Cutaneous sensory overlap across the mid-line for pain and touch for about 1·5 cm. was found to occur in the mid-line of the anterior thoracic and abdominal walls in subjects in whom the intercostal nerves on one side had been locally anæsthetized. Mid-line cutaneous overlap

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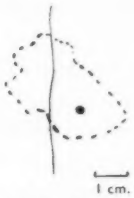

FIG. 3.—Experiment MN. Spread of 3 minims of 1/1,000 adrenalin hydrochloride solution injected intra-epidermally into the anterior abdominal wall. The straight line indicates the mid-line. The dot indicates the site of injection. The area of blanching recorded 20 minutes after injection is indicated by the interrupted line.

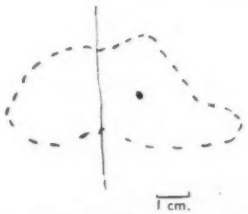

FIG. 4.—Experiment 29. The straight line indicates the mid-line of the anterior abdominal wall. The dot indicates the site where 1/10th of a minim of benzene was injected intra-epidermally. The interrupted line indicates the approximate extent of the resulting areas of flare and hyperalgesia recorded some 20 minutes later.

for pain and touch for about 1·5 cm. anteriorly in the neck was found after nerve section.

Cutaneous anæsthesia and analgesia were found delimited by the mid-line in the foreheads and faces of the two subjects in whom the whole trigeminal nerve root had been divided three and six months previously. In most of the patients in whom the supraorbital and supratrochlear nerves had been divided on one side pain and touch were not found to overlap the mid-line, but in some these sensations did overlap the mid-line for a few millimetres—not more than 5. It was not possible to produce sufficiently large areas of hyperalgesia and flare in the foreheads of two normal subjects to determine whether or not they would spread across the mid-line there—the areas were vertically disposed.

Local anæsthetics and the hyperalgesia.—When a small area of skin in the forearm or abdominal wall was infiltrated with procaine solution, the anæsthetic area being not more than 1·5 cm. square, and a small skin crush was placed within this area, a surrounding area of hyperalgesia did not develop until the local anæsthetic effect had worn off; when the crush was placed within a few millimetres of the anæsthetic area the

area of hyperalgesia surrounding the crush did not spread beyond the anæsthetized skin until the anæsthetic effect had passed off. Physiological saline solution or distilled water used instead of procaine solution did not have such effects. When 2 per cent procaine in physiological saline solution was injected around a cutaneous nerve within the distribution of which there was a hyperalgesic area, slight deformation of or friction to this area aroused pain immediately before and after the introduction of fine, sharp, steel needles into the epidermis and dermis, the application to the skin of von Frey hairs or a camel-hair brush, bending hairs and the application of warmed or cooled metal rods aroused no sensation whatsoever from the hyperalgesic as well as from the surrounding skin. The time required for the procaine solution to render hyperalgesia no longer detectable was somewhat longer than that required to obtain anæsthesia and analgesia to the stimuli just listed. During recovery from the regional nerve block there was sometimes a stage at which the subject reported either warm or cool stimuli as warm; at a later stage touch stimuli might be reported as tickling.

When anæsthesia of either the medial or the lateral cutaneous nerve of the forearm was complete, on the volar aspect of the limb the respective areas of skin from which no pain could be aroused were approximately 1 cm. smaller than the areas from which no touch sensation could be provoked. The margins of the latter areas coincided within the limits of experimental error. No cutaneous sensation other than pain could be aroused from the area of overlap. Skin injuries, produced as described above, in the area of skin from which pain only could be aroused provoked immediate pain which sometimes persisted and was followed within a few minutes by local reddening, whealing, skin hyperalgesia and flare surrounding and including the injury. The area of hyperalgesia was delimited on the side on which the nerve had been anæsthetized by the margin of the area from which no pain could be aroused. The time intervals between the infliction of the injury and the onset of the delayed reactions mentioned varied from ½ to 10 minutes. The sequence in which they occurred was usually that in which they are listed above. Skin injuries, by the methods stated, anywhere in areas rendered anæsthetic and analgesic by regional nerve block resulted in local reddening, whealing, and flare of the same degree and extent and at similar time intervals as in normal areas or in areas from which pain only could be aroused. Hyperalgesia and sometimes spontaneous pain were found present when analgesia no longer obtained in the injured area (fig. 1, Plate LIX).

Nerve injuries and the hyperalgesia.—In one subject the intra- and

sub-epidermal injection into the forearm of benzene in quantities of up to ½ a minim resulted in the production of seven ulcers extending into the superficial layers of the dermis. The developed ulcers and the surrounding skin were not hyperalgesic. From a small area of skin immediately distal to two of these ulcers pain only could be aroused. Crushing a fold of skin or the intra-epidermal injection of 1/10 of a minim of benzene or chloroform anywhere in the areas from which pain only could be aroused resulted in pain, local reddening, whealing, hyperalgesia and flare. The hyperalgesia and flare, after a little while, surrounded the ulcers—these did not have the barrier effect on the spread of hyperalgesia and flare shown by procaine; it was not certain that no cutaneous nerve plexus remained under the ulcer base (figs. 2 and 2*a*). Similar injuries to normal skin in the same forearm resulted in similar reactions of approximately the same extent and degree and with more or less the same time relations to the beginning of the experiment.

The hyperalgesia and the circulatory system.—Pain, either present spontaneously in or aroused by friction to or deformation of a hyperalgesic area, was found often to be more severe over subcutaneous veins. It was the skin itself that was so affected, and not the veins; the skin so affected could be lifted up from or moved over the veins quite easily in one rather thin subject. Superficial veins were found sometimes to delimit hyperalgesic areas of skin. Occasionally, areas of cutaneous hyperalgesia were found to extend along the superficial veins, either in a distal or in a proximal direction, or both. When the veins of the forearm were distended and the flow of blood in them arrested by surrounding the arm with a pneumatic cuff at a pressure of 60 to 70 mm. Hg, after 10 seconds to 2 minutes any skin hyperalgesia present in the forearm commenced to increase in severity, especially over distended veins, and spontaneous pain often appeared; these effects were more obvious during the first few minutes that the veins were occluded. The area of hyperalgesia often became somewhat larger and its extension along superficial veins very frequent (figs. 5, 6, 7, 8). The effects persisted for from a few seconds to several hours after releasing the venous circulation, apparently depending on the duration of the occlusion; the maximum time during which the venous circulation was arrested in the experiments in question was 15 minutes. Leaving the limb dependent was often found, after about ¼ of a minute, to lead to spontaneous pain in hyperalgesic areas; this pain disappeared, on emptying the veins, after a similar period of time. When the veins were emptied and the pressure in the pneumatic cuff was then rapidly raised from zero to 130 mm. Hg, thus arresting the arterial blood supply

FIG. 5.

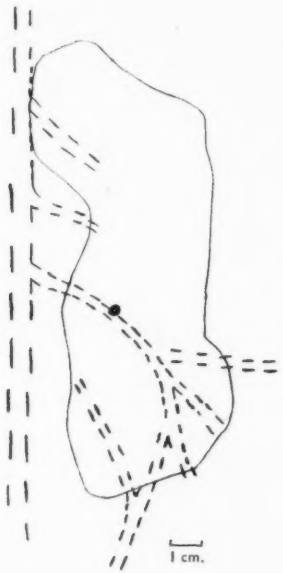

FIG. 6.

FIGS. 5 AND 6.—Experiment 36: FIG. 5.—Volar aspect of proximal part of forearm. The dot indicates the site where about 1/10th of a minim of benzene was injected intra-epidermally. The inner line indicates the area of hyperalgesia present 20 minutes later. The outer line indicates the extent of the area of hyperalgesia 12 minutes later still, after the venous circulation had been obstructed at the arm for 10 minutes. 30 minutes later the veins were again occluded at the arm. FIG. 6 shows the area of hyperalgesia recorded about 2 minutes later; the pain was then more severe, especially over obvious veins. The flare also seemed enlarged by the venous occlusion. Superficial veins are indicated by interrupted lines.

and maintaining the veins collapsed, after about ½ a minute the hyperalgesia began to diminish in degree and the area affected became smaller; the hyperalgesia usually regained its previous extent and intensity on releasing the circulation. The same results were obtained when the brachial artery alone was occluded. Arterial occlusion while the veins were distended led to variable results; sometimes the extent and degree of the hyperalgesia were reduced, although not as markedly as when the veins were collapsed; sometimes this reduction was followed by an increase in the degree of the hyperalgesia to its previous intensity; sometimes it became more severe. The reactive hyperæmia

FIG. 7.

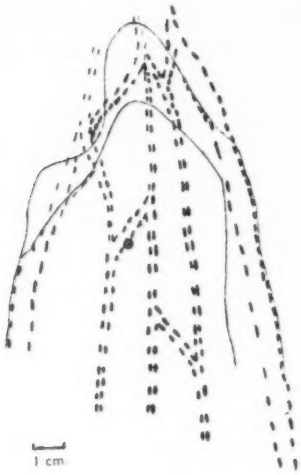

FIG. 8.

FIG. 7.—Experiment 2: Volar aspect of centre of forearm. The dot indicates the site where a small fold of skin was crushed with forceps. Superficial veins are indicated by the interrupted lines. The inner line shows the area of hyperalgesia present after 1 hour; it had stopped increasing in size. The veins were then obstructed at the arm; after 5 minutes, the hyperalgesia was more intense, and there was some spontaneous pain. The hyperalgesic area was now larger (outer line) and extended somewhat along veins.

FIG. 8.—Experiment 33: Volar aspect of forearm. Superficial veins are indicated by interrupted lines. The dot shows the site where 1/10th of a minim of benzene was injected intra-epidermally. The inner line indicates the proximal margin of the area of hyperalgesia present about 30 minutes later; it had stopped increasing in size. The outer line indicates the proximal extent of the area of hyperalgesia 5 minutes later still, during which the veins had been occluded at the arm.

that followed release of an obstructed arterial supply was sometimes accompanied by a temporary increase in the degree of the hyperalgesia, spontaneous pain sometimes being experienced.

In the human forearm, the intra-epidermal injection of adrenalin in the concentrations and quantities mentioned under the heading "Material and Methods" was found to produce an area of blanching which began to increase within a few minutes—sometimes less than a minute—of injection; at first it surrounded the site of injection in a roughly circular or oval manner, but after about 3 to 10 minutes it commenced and thence proceeded to assume a stellate shape. The processes

of the blanched area lay mostly, although not always, over obvious veins (fig. 9). The blanched processes of skin could be lifted up from

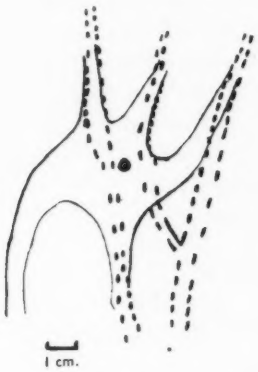

FIG. 9.—Experiment 12: Volar aspect of centre of forearm. The interrupted lines indicate superficial veins. The dot indicates the site at which slightly less than 2 minims of 1/1,000 adrenalin hydrochloride were injected intra-epidermally. The line indicates the area of blanching recorded 7 minutes later. There had been a small area of mild hyperalgesia near the site of injection. The area became larger, and the hyperalgesia became more intense, as the blanching appeared. Somewhat later, the veins were occluded. The hyperalgesia became still more intense, and the area spread along one of the proximal veins.

and moved over the veins. Blanching, presumably along lymphatic vessels, occurred first in a distal direction when the injection had been made near the elbow; when the injection had been made near the wrist the stellate processes of the blanched area developed first in a proximal direction; after about 3 to 20 minutes the blanched processes usually reached as far as 6 to 7 centimetres from the site of injection. In one series of experiments, the circulation was not impeded and the extent of blanching proximally was determined at given times. In one such experiment, for example, after 45 minutes the maximum spread of blanching proximally was 8 cm. from the site of injection. In another series of experiments the same amount of the same solution was injected intra-epidermally at the same site and the forearm was warmed to the same degree, but the arm was surrounded with a pneumatic cuff at pressures of from 65 to 150 mm. Hg. (The arterial systolic pressure of the subjects used was less than 120 mm. Hg.) Using the same region as in the example just described, after 30 minutes the maximum spread of the area of blanching, similarly measured, was 9 cm. Such findings were noted six times (figs. 10 and 11). If, at

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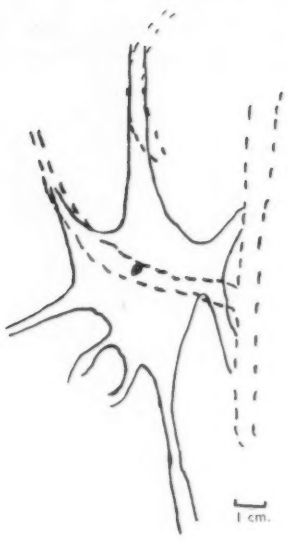

FIG. 10.

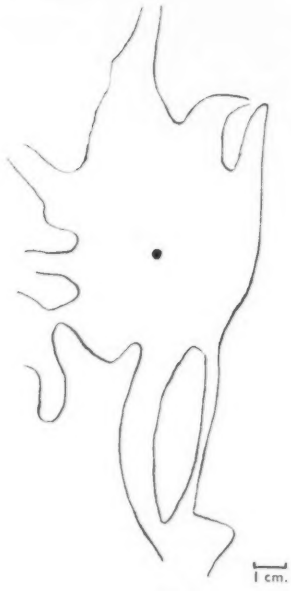

FIG. 11.

FIGS. 10 AND 11.—Experiment 35 : Dorsal aspect of forearm. The dot indicates the site where 2 minims of 1/1,000 adrenalin hydrochloride were injected intra-epidermally. The interrupted lines indicate superficial veins. The line in fig. 10 indicates the area of blanching recorded after 45 minutes. Next day, a similar injection was made at the same site, but the veins were occluded at the arm. The line in fig. 11 indicates the area of blanching recorded after 30 minutes.

previous or subsequent dates to those of the foregoing experiments, a small fold of skin was crushed at the same site where the vasoconstrictor substance was or would be injected, and the effect of venous occlusion on the resulting hyperalgesia was determined, it was found that the area of hyperalgesia often spread along but one or a few of the veins related to the region involved. No stellate spread of the area of hyperalgesia was observed other than over obvious veins.

In the anterior abdominal wall, the intra-epidermal injection of adrenalin solution resulted in an oval area of blanching, disposed transversely, rapidly spreading across the mid-line (fig. 3, page 638).

In a normal forehead intra-epidermal injection of approximately 1·5 minims of 1/1000 adrenalin about 1·3 cm. from the mid-line, about 2·5 cm. above the eyebrows, resulted in an area of blanching, vertically disposed, that spread upwards over superficial veins beyond the hair-line (about 4 cm. above the site of injection) within 2 minutes; some 7

minutes later the area of blanching extended lateralwards and downwards in stellate fashion, mainly over superficial veins; spread across the mid-line—for about 5 mm.—occurred only in a small area at the hairline, along a vein that also crossed the mid-line. The area of blanching proceeded to become smaller after some 12 minutes. The shape and disposition of the area of blanching were similar to, but larger than, areas of flare and hyperalgesia previously produced by injuries at the same site at which the adrenalin was injected; the adrenalin injection produced rather more pain at and near the site of injection than a similar amount of distilled water similarly injected previously at the same site.

The spread of the adrenalin was not prevented by intra- and subepidermal infiltration with procaine solution.

The sub- or intra-epidermal injection of a small amount of aqueous adrenalin hydrochloride solution—e.g. ½ to 2 minims of a 1 : 1,000 concentration—into an area of cutaneous hyperalgesia resulted in an increased degree of hyperalgesia in the blanched zone. The more severe area of hyperalgesia increased in size *pari passu* with the development and spread of the zone of blanching within the boundaries of the original region of hyperalgesia. The increase in the degree of hyperalgesia was sometimes such that spontaneous pain was experienced. In one subject a crush of a small fold of skin did not always result in an area of hyperalgesia. The sub- or intra-epidermal injection of 1 minim of 1 : 1,000 aqueous solution of adrenalin hydrochloride at a site such that the area of blanching included the crushed skin then often resulted in hyperalgesia. The sub- or intra-epidermal injection of aqueous atropine or acetylcholine solutions—amounts employed were 1 to 3 minims containing 1/300–1/100 grain of atropine sulphate and 2 to 5 minims containing 0·03–0·1 gramme of acetylcholine—into an area of hyperalgesic skin resulted in a diminution in the degree and sometimes in a disappearance of hyperalgesia in the resultant flushed skin. Warming the forearm sufficiently to produce cutaneous vasodilatation after a few minutes or sometimes slightly less than a minute had similar effects. Cooling the forearm so as to produce vasoconstriction resulted, after a few minutes, in an increase in the intensity of the hyperalgesia, and sometimes in spontaneous pain.

Discussion

Neural mechanism of the hyperalgesia, flare and inflammation.—The effects of local anæsthetics on the development of cutaneous hyperalgesia following small skin injuries suggest that a neural mechanism is

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involved in the reaction; Lewis (1936) found this mechanism to be peripheral, a conclusion not supported by Hardy, Wolff and Goodell (1952), who do not, however, I think, refute it factually and finally.

The observations on the relations of hyperalgesia and flare to the mid-line were thought previously (Harpman, 1948) to indicate that there must be spread of a substance in the production of these reactions; the further observations presented here show that a peripheral neural mechanism may also explain the phenomena in question. Foerster (1933) describes vasodilatation produced by faradization of a posterior spinal nerve root sometimes extending across the mid-line of the chest or abdomen for about 1 in.

There is evidence that a nervous process takes part in the vascular changes of inflammation (Krogh, 1920, 1922; Bruce, 1913, 1910; Bardy, 1915; Breslauer, 1919), and that this process, like flare (Lewis, 1927, 1936; Lewis and Grant, 1924; Lewis, Harris and Grant, 1927; Lewis, Grant and Marvin, 1927), is dependent upon the presence of regional nerve fibres and endings that have been divided from their nerve cells not more than 5 to 7 days previously. Tolnick and Beck (1945) and Loeser (1938) have based a clinical test on the fact that histamine introduced into the skin does not produce flare when the nerves to the part have degenerated. (While a neural mechanism is concerned in vascular phenomena of inflammation, some of these occur also in the absence of a nerve supply (e.g. Doupe and Cullen, 1943; Menkin, 1940; others quoted by them)—the equivalent, perhaps, of Lewis' local reddening). Regarding the neural mechanism of flare: Kuntz and Hamilton (1938), Woollard, Weddell and Harpman (1940), Weddell and Pallie (1954) and others have shown the close relation between sensory cutaneous nerve-endings and skin vessels, including capillaries and lymphatics. Fig. 12 is a photomicrograph of a methylene-blue preparation of human skin made by the late Professor H. H. Woollard, illustrating particularly plainly the intimacy of the relations between an organized cutaneous sensory nerve-ending and surrounding capillaries. Regarding axon reflexes: Woollard, Weddell and his colleagues and I have observed the prolixity of axon branching, but have failed, in methylene-blue spread preparations of many parts of the bodies of various mammals, to see an axon terminating in two different tissues.

The nerve fibres and endings concerned.—The observations recorded in this paper also indicate that the nerves involved in the hyperalgesic reaction described are those that subserve pain. That the sympathetic nervous system is not essential to the production of hyperalgesia and

flare by epidermal injuries was also found by Lewis (1936, 1937*a*). The conception that free nerve-endings subserve pain exclusively (Woollard, Weddell and Harpman, 1940) is now untenable; in at any rate certain situations and circumstances, such endings subserve also touch, warmth and cold (Harpman, 1951; Zander and Weddell, 1951; Weddell and Sinclair, 1953; others); the observations of Bell and Karnosh (1949) on a case of cerebral hemispherectomy indicate the importance of the central connexions of peripheral sensory nerve fibres and endings in interpreting the nature of a stimulus, and those of Weddell, Taylor and Williams (1955) suggest that the spatial and temporal pattern of the nerve impulses is similarly concerned.

It is known that nerve fibres subserving touch, cold, warmth, pain, etc., are affected differently by asphyxia or local anæsthetics. Lewis (1937*b*) used such observations to support his view that hyperalgesia, flare and pain, and the other sensations also, are all subserved by different sets of nerve fibres and endings. The observations reported in this paper suggest that there may be other explanations for Lewis's findings, a contention supported by the observations of Sinclair and Hinshaw (1951*a*, *b*; 1950*a*, *b*) on the effects of procaine, cooling and compression nerve blocks, and of Merrington and Nathan (1948) on post-ischæmic paraesthesiæ. The effects of asphyxia and local anæsthetics on nerves are very complex and probably not susceptible of a simple explanation; vasomotor tone, and probably chemical changes, are also concerned. Dodt and Zotterman (1952) and Hensel and Zotterman (1951) have shown that nerve fibres and perhaps receptors that respond to cool or warm do not respond to touch or pressure, but those that usually respond to cool may also be stimulated by heat, and cooling may excite nerve fibres that usually respond to pressure and touch.

Hyperalgesia and hypoæsthesia.—That hyperalgesic areas are hypoæsthetic was also observed by Trotter and Davies (1909), Riddoch (1938), Lewis (1936), Rivers and Head (1908), Lewis and Pochin (1938). This may be due to changes in the potassium and calcium content of the skin (Feng, 1933; Hoagland, 1933, 1934, 1935, 1936; Rubin, 1936; Hoagland and Rubin, 1936; Talaat, 1933; Dun and Finley, 1938; Brink, 1951), to central inhibition (Zotterman, 1939), or to anatomical reasons: Weddell and Harpman (1940) and many others quoted by them have found that many encapsulated or complex nerve-endings are supplied also by accessory nerve fibres with free nerve terminals.

Possible humoral mechanism of the hyperalgesia. The observations recorded above suggest that small skin injuries produce or liberate one

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or more substances that, diffusing, result in hyperalgesia of skin surrounding the injury. Lewis (1936, 1937*a*, 1942) considered this explanation incorrect owing to the relative speed with which the hyperalgesia surrounding the injury developed and because the spread of the hyperalgesic area was sometimes greater in a distal than a proximal direction. Comparison of the observations on hyperalgesia and on the spread of adrenalin injected intra-epidermally reported in this paper indicate that these objections are invalid.

The circulatory system and the hyperalgesia.—That cutaneous hyperalgesia is often more severe over subcutaneous veins, that it spreads along such veins distally and proximally, that hyperalgesic areas are often delimited by superficial veins, that the hyperalgesia can be made worse by venous distension, was known also to Trotter and Davies (1909), Lewis and Hess (1933) and Lewis (1936, 1942). Trotter and Davies suggested that a substance causing hyperalgesia results from degeneration of divided nerves. Lewis and Hess thought that the hyperalgesia and spontaneous pain produced by cutaneous injuries was due to the liberation by injury of a substance, and that the relations of this hyperalgesia and spontaneous pain to superficial veins was explainable by the presence of this substance and by stretching of the skin through engorgement of vessels. Lewis and Zotterman (1926) found that ultra-violet irradiation and freezing of skin produced vasodilator substances that diffused through tissue spaces and lymphatics. Lymphatics are anatomically closely related to blood vessels, especially veins and capillaries (Clark and Clark, 1937; Henry, 1933; Testut, 1929; Drinker and Yoffey, 1941; others). Obstruction of the veins of a limb increases the flow of lymph from it (Starling, 1941; Drinker and Yoffey, 1941; White, Field and Drinker, 1933). White *et al.*, Devenish and Jessop (1940) and Kinmonth (1952) have also shown the remarkable speed with which substances injected intracutaneously and subcutaneously spread through lymphatics. Haynes (1932) found that acetylcholine increased, and adrenalin first increased and then decreased the flow of subcutaneous lymph in the dog. McMaster and Hudack (1934, 1933, 1937) and Hudack and McMaster (1933) have found that the least cutaneous scratch, even one that does not penetrate through the epidermis, results in lymphatic absorption from the abraded surface; normal flow along cutaneous lymphatics is so rapid that it may reach from the forearm to the axilla in a few minutes; lymph flow is increased by warming or elevating the part; the permeability of lymphatics is increased by mechanical, chemical, bacterial or thermal irritation and by histamine. Abramson and Engel (1938) found that they could accelerate

the absorption of dyes or blood in the skin by producing a histamine or allergic wheal. Abramson and Gettner (1941) have suggested that histamine or adrenalin introduced into the skin electrophoretically enters lymphatics, courses through them and then escapes from them into surrounding tissues and shows its effects, a suggestion supported by the observations of Miles and Miles (1952). The present observations may be considered in conjunction with these facts. A likely conclusion would seem that the development of areas of cutaneous hyperalgesia many centimetres square around skin injuries but a few millimetres square is due to the production or liberation, and the spread through tissue spaces and lymphatics, of one or more substances.

The observation that adrenalin increased the hyperalgesia is perhaps most readily explainable by the vasoconstrictor effect of the adrenalin; Kellgren, McGowan and Hughes (1948) have found that cold aggravates deep hyperalgesia; on the other hand, it should be borne in mind that Buelbring and Whitteridge (1941) found that adrenalin may reduce the threshold of nerve stimulation, and that Leimdorfer and Metzner (1949) and Ivy *et al.* (1944) have found that epinephrine injected intracutaneously, intravenously and intracisternally or injected into the carotid artery in animals produces analgesia or even anæsthesia. The observations with atropine, acetylcholine and warming suggest that improving the blood flow reduces the hyperalgesia. Vasodilators relieve trigeminal neuralgia (e.g. Karl, Peabody and Wolff, 1945; others) and other pain syndromes (Harpman, 1948; others quoted by him). Both chemical and mechanical factors may be concerned in the relationships between the circulation and hyperalgesia. Mayfield (1951) considers that in causalgia due to nerve lesions, the disturbance is due to a synaptic shunt between sympathetic and sensory nerve fibres; administering adrenalin to patients suffering from causalgia he found makes the pain worse. It seems unlikely—but possible—that such a process, perhaps with a chemical rather than a mechanical "shunting" basis, is concerned in some of the phenomena discussed in this paper.

The close interrelationships between skin hyperalgesia and flare noted in the observations presented in this paper were also noted by Lewis (1936, 1937*a*, 1942).

Hardy, Wolff and Goodell (1952) consider hyperalgesia due to a neural mechanism, and do not subscribe to the view that the production or liberation and the spread of a substance are involved. They ignore the relationship of areas of cutaneous hyperalgesia to superficial veins—a relationship that occurs with a frequency such that it cannot be ascribed

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merely to coincidence. They state that methylene-blue infiltrated into skin does not spread sufficiently fast and extensively to support a humoral origin for hyperalgesia from skin injuries. Methylene-blue is decolorized by living tissues; hence, it is not a suitable substance for investigating this particular problem; I have tried it, and found it far less reliable than adrenalin. They ignore observations showing how remarkably rapidly and extensively dyes, adrenalin and histamine introduced into the skin can spread through tissue spaces and lymphatics, and do not consider the fact that the hyperalgesia following a skin injury is less severe farther from the injury than near it.

Conclusions

Conclusions that may be drawn from the observations reported and discussed above include:

(1) Skin injuries a few millimetres square may become surrounded by areas of cutaneous hyperalgesia and flare many centimetres square.

(2) A peripheral neural mechanism is concerned in the production of cutaneous hyperalgesia by skin injuries. The nerve-endings and fibres concerned are those that subserve pain. These are free nerve terminals borne by thin nerve fibres. Such nerve fibres and endings, in certain situations and circumstances, subserve also sensations other than pain, the pattern of the central connexions being involved.

(3) Cutaneous hyperalgesia is often more severe over subcutaneous veins; areas of such hyperalgesia are sometimes delimited by superficial veins and may extend along them proximally, distally or both. Venous obstruction makes such hyperalgesia worse. These features, and the disposition of areas of skin hyperalgesia, seem due to the spread, through tissue spaces and lymphatics, of one or more substances freed or produced by skin injury and causing cutaneous hyperalgesia, and to vascular engorgement.

(4) Hyperalgesic areas are hypoæsthetic. There may be chemical as well as anatomical reasons for this.

PART II

Problems that Emerge from the Above Conclusions

Of the many problems that emerge from the above conclusions, two especially have aroused our interest:

(1) what is the nature of the substance—or substances—that probably produces or produce hyperalgesia and flare following skin injuries?

(2) how can the views of a chemical and a neural mechanism of hyperalgesia and flare so produced be harmonized?

This part deals with observations made with a view to answering these questions.

Material, Methods and Results

Observations were made on the forearms and anterior abdominal walls of the two authors. There were injected intra-epidermally 0·01 to 0·05 mil. of various solutions and suspensions listed hereunder with their effects and the significance ascribed to the results. Each preparation was tried at least twice. When it was desired to compare results obtained with various substances care was taken to use similar quantities. Some of the preparations were cultured bacteriologically.

1.

Human epidermis was obtained from patients on whom split skin graft operations were being carried out. Pieces of epidermis with dermis of the external auditory meatus and pieces of temporal muscle were obtained during aural operations. The skin and muscle so obtained were crushed in a small amount of distilled water and the supernatant fluid was used for injection. The injections were made either on the same day or on the day after the material was obtained; sometimes the material was kept frozen overnight before being prepared. As a control, similar quantities of distilled water and normal saline solution were employed.

Results.—Intra-epidermal injection of up to 0·05 mil. of either distilled water or the preparations of epidermis or muscle resulted in immediate smarting and was followed within a few seconds by the production of flare and a surrounding area of cutaneous hyperalgesia several centimetres square; the flare and hyperalgesia disappeared within some five minutes. Intra-epidermal injection of 0·02 mil. of the preparation of epidermis with dermis resulted in immediate severe smarting, flare and hyperalgesia lasting not more than five minutes; the areas involved were much larger, and the reactions were much more intense than when water or epidermis only or muscle, in similar concentrations, even if in larger quantities, was used. The hyperalgesia was more severe at and near the site of injection and gradually faded in intensity towards the periphery of the hyperalgesic area. When epidermis or epidermis and dermis were used, often, but not always, there developed, some one or more hours later, pain, swelling, redness, hyperalgesia; these delayed reactions may have been due to bacterial contamination. Intra-epidermal

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injection of 0·05 mil. of normal saline solution produced a very little momentary discomfort; the area of injection became surrounded within a few seconds by a flare.

Comment.—These observations suggest that there may be in the deeper layers of the epidermis or/and in the dermis one or more substances that are concerned in the production of pain, hyperalgesia and flare; it is, of course, not established that this is the same substance or substances that produce these reactions on injuring skin. The hyperalgesia and flare following injection in these experiments lasted not more than five minutes; those following small skin injuries often last many hours. It may be, therefore, that when skin is injured so that hyperalgesia and flare develop a substance keeps or substances keep on being produced or freed from the injured skin for almost as long as the hyperalgesia and flare last. Lewis (1936) found that intradermal injection of small quantities of aqueous extracts of freshly excised and crushed human or guinea-pig skin produced hyperalgesia and found that this result was not due to changed ph or altered tonicity of the extract, nor to its containing protein, potassium, histamine or acetylcholine.

2.

Preparations of epidermis with dermis such as mentioned under 1 were tested after

(*a*) boiling for ten minutes

(*b*) incubating for four hours at 37° centigrade.

Results.—Boiling or the incubation had no effect on the production of smarting, flare and hyperalgesia lasting some eight minutes following intra-epidermal injection.

Comment.—These results suggest that the phenomena observed were not due, at any rate directly, to enzyme action—but such action might have occurred when the skin was removed.

3.

Some grey and white matter of human brain was obtained at a neurosurgical operation; it was mushed up with a little distilled water in a mortar and pestle; supernatant fluid was employed for injection.

Result.—The injection caused slight smarting, flare and hyperalgesia lasting but a few minutes and very definitely less severe than when whole skin was employed.

Comment.—This result suggests that the effects of employing whole skin were probably not due to the nervous tissues contained in it.

4.

1 per cent aqueous trypsin solution was injected.

Result.—This caused local reddening, flare and slight hyperalgesia, no more severe than those produced by distilled water.

5.

B.D.H. fibrin was triturated with a little water, N/500 HCl solution added so as to bring the mixture to pH2 and pepsin added to 1 in 10,000. Quantities of the supernatant fluid were injected intra-epidermally both before and after incubation at 37° centigrade for three hours.

Result.—The material without incubation produced, on intra-epidermal injection, some smarting for a minute or two, little more than distilled water.

The incubated material caused, on similar injection, severe smarting as soon as the injection was commenced, but the smarting disappeared within two minutes and the area was at no time thereafter painful or hyperalgesic. About an hour after injection there developed an area of cutaneous reddening and swelling, approximately 1 cm. in diameter, which took about three days to disappear; bacterial cultures of the material revealed microbial contamination.

Comment.—The incubated type of material prepared as mentioned above has been shown by Spector (1951), Duthie and Chain (1939) and Cullumbine and Rydon (1946) to contain polypeptides that produce the vascular phenomena of inflammation. Duthie and Chain have also tried their polypeptide preparations on human skin and produced localized reddening and whealing, but no flare and no pain.

6.

Human blood fibrin was obtained from one of the authors. To it there was added 1 per cent trypsin and it was then incubated at 37° C. for from two to thirty-six hours. The supernatant fluid was then employed for injections.

Results.—Material incubated for two hours produced slightly more pain and hyperalgesia than 1 per cent trypsin solution alone; the flare and hyperalgesia appeared within some 30 seconds of the injection and disappeared within some 3½ minutes. With the material incubated for sixteen hours a similar reaction occurred. However, in both these sets of experiments there occurred some hours later, and lasting for a day, swelling, redness and considerable hyperalgesia, more severe when the incubation had lasted for sixteen hours.

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When the material had been incubated for thirty-six hours the injections were either painless or accompanied by smarting but were followed within a few seconds by flare, severe pain and hyperalgesia over a considerable surrounding area (of about 4 × 8 cm. and transversely disposed on the anterior abdominal wall). The hyperalgesia and pain began to pass off after some two minutes and had disappeared some 3 to 8 minutes after injection. Some one and a half to four hours after giving the injections there developed redness and swelling over areas some 3 × 6 cm. around the sites of injections and these areas became exceedingly painful and hyperalgesic; these delayed reactions lasted for about two days; in a limited number of observations it was apparently not possible to desensitize against their occurrence and it was thought unwise to continue with these experiments, which might possibly lead to dangerous reactions. This reaction occurred whether the blood fibrin had been prepared from the blood of the subject into whom the injection was made or not.

Bacteriological cultures of the material revealed microbial contamination.

Seitz filtration of the material resulted in the intradermal injection producing less pain than, and an equally mild flare as, distilled water similarly injected.

Comment.—The findings suggest that the material employed in these experiments, especially that incubated for thirty-six hours, contained a substance that produced the pain, hyperalgesia, redness and swelling of inflammation, and that these reactions were not of allergic nature, but that at any rate the late reactions were due to bacterial infection. Seitz filtration of the material may have abolished the reactions, not only by eliminating bacteria, but perhaps also by eliminating larger molecules.

7.

Distilled water containing histamine 1 in 1,500 and acetylcholine 1 in 50 was injected intra-epidermally in quantities of up to 0·05 mils., or deposited on the surface of the skin and pricked through two or three times to a depth such as to obtain some drops of blood.

Result.—No burning pain was produced by such procedures in either subject.

Comment.—These experiments did not support the finding of Emmelin and Feldberg (1947) that burning pain is produced by such a solution introduced into the skin. Rosenthal and Sonnenschein (1948)

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also did not confirm this finding of Emmelin and Feldberg. Harpman (1950) could not confirm the opinion of Rosenthal and Minard (1939), Rosenthal (1950) and Rosenthal and Sonnenschein (1948) that histamine is a "pain substance."

8.

Human blood fibrin incubated with trypsin for twenty-six hours was injected intra-epidermally after adding to it some fresh, crushed, brain matter.

Result.—This injection caused smarting that passed off after some seconds. The flare that appeared about a minute after injection was less in degree than that which resulted from injecting a similar amount of trypsin digest of fibrin not diluted with crushed brain matter.

Comment.—This experiment does not help us in integrating the views of a neural and a chemical process in the production of flare and hyperalgesia.

9.

There was injected intra-epidermally blood fibrin with trypsin incubated for twenty-six hours at 37° centigrade to which a small amount of 2 per cent procaine had been added.

Result.—The addition of the procaine prevented the development of flare for as long as the anæsthesia and analgesia lasted. Observations on hyperalgesia in these experiments were useless because the subjects concerned always developed hyperalgesia at the site of procaine injections after the anæsthetic and analgesic effects of the procaine had worn off.

Comment.—This observation may suggest a link between the views of a chemical and a neural mechanism of flare (Lewis, 1927).

10.

0·05 mil. of serotonin creatinine sulphate (kindly supplied by Abbott Laboratories, Chicago) were injected intra-epidermally; concentrations employed were similar (10^{-8} g/ml) and thirty times greater than those employed by Armstrong, Dry, Keele and Markham (1953).

Results.—The injections resulted in smarting for a few seconds and, in one instance, slight hyperalgesia of the area of injection lasting about one minute. A slight flare occurred around the area of injection. There was no further reaction.

Comment.—These observations do not support the suggestion of Armstrong *et al.* (1952, 1953) that serotonin creatinine sulphate is the pain-producing substance.

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II.

Areas of hyperalgesia were produced in the forearms by methods described in Part I of this paper. Into such areas there were injected sub-epidermally 0·5 mil. of distilled water and 0·5 mil. of distilled water containing 1/30 of a grain of strychnine sulphate.

Results.—The distilled water injections were painful for the first three or four minutes, but thereafter the hyperalgesia was somewhat less over an area of approximately 1·5 × 1·5 cm. about the site of injection. Injection of distilled water containing strychnine was painless and some two minutes after injection an area approximately 1·5 × 1·5 cm. was no longer hyperalgesic and was found to be hypoæsthetic and hypoalgesic to pin-pricks, touching with a camel-hair brush, cool and warmth; this did not obtain where water only had been injected. Hyperalgesia did not return in the area where the strychnine solution had been injected.

It was further found that if 1 millilitre of distilled water containing 1/30th of a grain of strychnine sulphate was injected sub-epidermally into the forearm and some 10 to 15 minutes later the skin of this area was traumatized by the methods mentioned in a previous study (Harpman, 1948) the resultant hyperalgesia was considerably less severe than that produced by similar injuries, at other times, in the same part of the body, without first using the strychnine solution.

Comment.—These observations do not support and, in fact, may be considered to refute the findings of Hellauer and Umrath (1948), who claim to have isolated from dorsal spinal nerve roots a substance that they consider is concerned with the transmission of sensory nerve impulses and with antidromic vasodilatation and flare; it was neither acetylcholine nor histamine and was destroyed by an enzyme contained in the dorsal nerve roots, the enzymic action was arrested by strychnine but not by eserine; observations of Holton and Perry (1951) do not confirm this alleged effect of strychnine.

Discussion and Conclusions

The observations presented above suggest that when skin is injured there may be produced in the deeper layers of the epidermis and/or in the dermis one or more substances that are concerned with the production of pain, hyperalgesia and flare, and that this substance keeps or substances keep on being produced or freed from the injured skin for almost as long as the reactions in question last. The observations also suggest that the substance or substances may result from protein disintegration, probably by enzymic action, as suggested by findings of

Armstrong *et al.* (1952, 1953) on *fresh* skin blister fluid and of Spector (1951) and others on inflammation, but may result from bacterial infection. In many attempts we were unable, with the facilities available to us, to prepare blood fibrin digests entirely aseptically. Perusal of texts on bacteriology indicates that the chemistry of pain in bacterial inflammation is not known. In rats and rabbits, polypeptides injected intradermally produce vascular reactions of inflammation in from 1 to 30 minutes (Spector); these times may be compared with those of the hyperalgesic reactions discussed in Part I. Either the "immediate" reactions following intra-epidermal injections are not due to bacterial contamination, or the results of such experiments on the vascular phenomena of inflammation by Spector, Duthie and Chain, Rydon and Cullumbine and others are also suspect, as they did not use bacteriological controls. Proteins are readily carried by lymph (Drinker and Yoffey, 1941). Figs. 6, 7, 8, 9, 10 and 11 show that extension along veins of the blanching of adrenalin injected intra-epidermally is greater than that of areas of cutaneous hyperalgesia; Miles and Miles (1952) have found that histamine injected intradermally spreads more readily along lymphatic channels than the polypeptide leukotaxine.

Hyperalgesia following inflammation and trauma may be due to changes in the *balance* of organic and/or inorganic tissue components.

Stoner and Green (1945) have suggested that adenosine triphosphate may be one of the substances concerned in the reactions that follow limb ischæmia; the quantities used in their experiments seem too large for this substance to be the one concerned with the hyperalgesia considered in this paper.

The Fundamental Problem

There is support for the view that a central excitatory state is concerned in the production of some pain syndromes and forms of hyperalgesia (e.g. Livingston, 1943; Hardy, Wolff and Goodell, 1952); thus, for instance, prefrontal leucotomy comes to be required in some cases of pain syndromes in which more distal sections within the neuraxis have failed. Lewis' finding that a peripheral neural process is concerned in the production of flare and cutaneous hyperalgesia has not been factually refuted. Evidence has also been elaborated in this paper in favour of a humoral process in the production of cutaneous hyperalgesia and flare. So far, these various views have not been unified. The desire—unfulfilled—to integrate the views of chemical and neural mechanisms of flare and hyperalgesia is also manifest in Sir Thomas Lewis's writings. It is hoped that this contribution may provide pointers towards the solution of this problem.

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LEGENDS TO PLATES

PLATE LIX

FIG. 1.—Volar aspect of forearm. The x indicates where procaine was injected around the lateral cutaneous nerve. The two straight lines delimit the area from which cutaneous pain only could be aroused when anæsthesia of the nerve was complete. The dot indicates the site of a skin crush; the heavier oval outline indicates the resulting area of hyperalgesia while the anæsthetic was fully effective; the thinner line shows the extent of the hyperalgesic area when the anæsthesia had worn off.

FIG. 2.—Experiment 64. Ulcer on dorsal aspect of forearm. From the area of skin distal to the ulcer delimited by the inner line pain only could be aroused. 0 minute: a fold of skin within the above mentioned area was crushed with a forceps. After 8 minutes: there had developed areas of flare and hyperalgesia approximately delimited by the outer line distal to the ulcer. After 15 minutes: the hyperalgesia and flare had spread proximal to the ulcer as shown by the line proximal to it.

FIG. 2A.—Experiment 60. Ulcer on volar aspect of forearm. The distal margin of the ulcer was anæsthetic and analgesic. From the small area of skin distal to the ulcer delimited by the inner line pain only could be aroused. A fold of skin within this area was crushed with forceps. The distal and the proximal inner and outer lines show the approximate limits of areas of hyperalgesia and flare present about 15, 20 and 25 minutes later.

PLATE LX

FIG. 12.—Photomicrograph of a methylene-blue preparation of human skin made by the late Prof. H. H. Woollard, showing the close relations between an organized sensory nerve-ending and capillaries.

PLATE LIX

FIG. 1.

FIG. 2.

FIG. 2A.

To illustrate article by J. A. Hartman and T. P. Whitehead

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PLATE LX

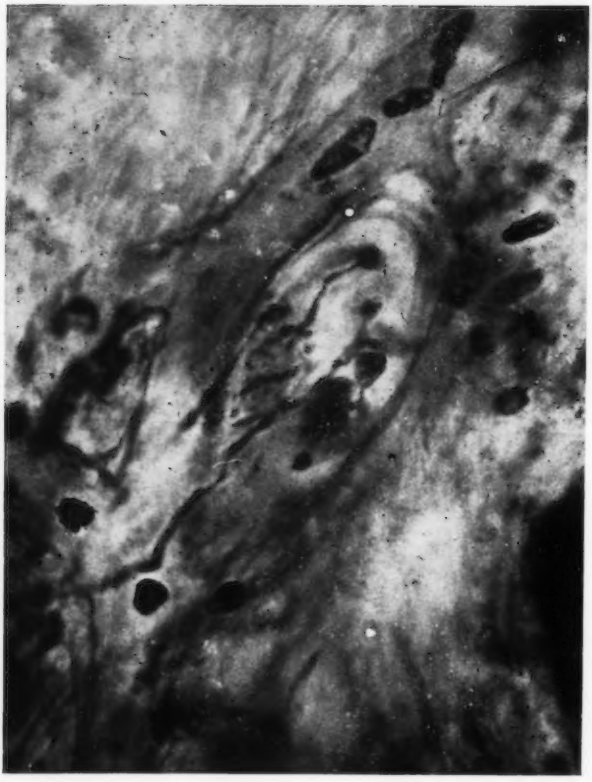

FIG. 12.

To illustrate article by J. A. Harpman and T. P. Whitehead

AXON SPROUTING IN PARTIALLY DENEUROTIZED NERVES

BY

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INTRODUCTION

IN a disease such as poliomyelitis, whether in man or in experimental animals, the death of the anterior horn cell produces, in the peripheral nerve trunk, a situation where normal intact nerve fibres are contained in the same nerve bundle and in close contiguity with degenerating nerve fibres. A similar situation can also be produced experimentally in a peripheral nerve trunk by choosing a nerve that has contributions from, say, three different nerve roots and deliberately cutting one of the contributing roots. This experimental procedure will produce partial deneurotization of the nerve and partial denervation of the muscle.

A somewhat similar situation can be produced at the periphery by choosing a muscle innervated by two nerve trunks, and cutting one of these trunks so as to produce partial denervation of the muscle. The production of collateral and ultraterminal outgrowth of fibres from the intact nerves in these conditions of partial denervation of skeletal muscle is well established (Edds 1950; Hoffman 1950; van Harreveld 1952). The outgrowths have been shown to take place usually from the nodes of the terminal millimetre of the motor axon. Occasionally, however, collaterals have been detected at somewhat greater distances than a millimetre.

The level at which sprouting of new axons occurs in the partially deneurotized nerve trunk is much more doubtful. Edds (1949) failed to detect new fibres in the partially deneurotized nerve trunks and concluded that sprouting only occurred in the intramuscular branches of these trunks. This study was conducted on osmic treated nerve and therefore relates only to the formation of new myelinated fibres.

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This apparent absence of sprouting following partial deneurotization of a nerve trunk seemed rather puzzling in the light of the older evidence (Perroncito, 1905) that collateral sprouts are formed in large numbers from the fibres of the central stump of a sectioned nerve within twelve hours of section. The inability to find new axons in denervated muscle that were unconnected with end-plates and the relatively late time of first detection of sprouts in these preparations, also suggested a failure to detect these new fibres when first formed.

With increasing evidence of the existence of submicroscopic fibres in the peripheral nervous system (Fernández-Morán 1952, 1953) and more detailed information regarding the non-myelinated fibres and their distribution and relation to the Schwann elements, derived from electron microscopic studies (Gasser 1955, Causey and Hoffman 1954, 1955*a*) we have been prompted to re-examine this problem of sprouting in main nerve trunks by electron microscopic methods.

Material and Method

The material was taken from a strain of hooded rats, 35 animals were used. Partial deneurotization of the sciatic nerve was carried out by section of L5, under intraperitoneally administered nembutal, 35 mgm/kgm, followed by resection and retraction of the cut ends, leaving a gap of approximately 5 mm between them. Under these conditions previous experience has indicated a delay of twenty-one days or more before regenerating fibres bridge the gap. The sciatic nerve in mid-thigh, and tibial nerve from below the knee, as well as intact nerve roots L4 and 6, were studied.

19 animals in all received pyronin treatment (0·1 per cent in drinking water) as in a previous study (Hoffman, 1952). Operated and control nerves were removed and prepared from twenty-four hours to twenty-one days after operation. Most of the material has been studied by electron microscopy, the material being fixed in Palade's buffered 1 per cent osmium tetroxide, at pH 7·2–7·4, for a period of four hours at room temperature, but later at 4° C. Tissues were embedded in butyl methacrylate, and sectioned at 250–500 A.U. on a Cook and Perkins thermal expansion ultra-microtome. Sections were examined in a Metropolitan-Vickers E.M.4 microscope, with a 50 μ objective aperture.

Two sets of nerves, from animals killed fourteen and twenty-one days after operation, fixed in 10 per cent formalin, were sectioned at 5 μ and stained by Holmes (1947) silver method.

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Observations

The general arrangement and relationship of nerve fibres with Schwann cells and the endoneural collagen have been discussed in previous papers (Causey and Hoffman 1954, 1955*a*) and will therefore be considered only briefly here. Both myelinated and non-myelinated fibres are enclosed within Schwann cells, as may be seen in fig. 1, from the vagus nerve (it should be pointed out that the number of non-myelinated fibres in normal rat tibial nerve is so small that illustration from that source is inadequate). The non-myelinated fibre is often connected with the Schwann cell membrane by a double-layered connecting membrane or mesaxon : such mesaxons can be seen in several places in fig. 1. Numerous non-myelinated fibres lie within a single Schwann cell, sometimes closely packed in the cytoplasm. Occasionally what is taken to be the point of entry of the fibre into the cell is seen : at this point the Schwann cell membrane is invaginated around the axon, forming a funnel-like arrangement.

Degenerative changes in the interrupted myelinated fibres may be detected after two or three days : the axon becomes coarsely striated due to aggregations of the fibrillæ, and then the axoplasm breaks down into irregular particles, as seen in fig. 2. The myelin becomes less regular in arrangement, portions protrude into the axon, and clefts appear. Meanwhile the Schwann cells hypertrophy markedly, the nuclear membrane becomes irregular in outline, and the mitochondria are replaced by numerous hollow vesicles, a process resembling that observed in ganglion cells in the active stage of restitution following chromatolysis (Causey and Hoffman, 1955*b*). Eventually, between the surviving myelinated fibres, numerous columns of empty Schwann cells may be seen.

As early as twenty-four hours after operation groups of tiny (from 0·1 μ upwards) fibres may be seen lying in their Schwann cells between surviving myelinated fibres. After longer post-operative periods, increasing numbers of such bundles are found, packing the spaces between the myelinated fibres, as seen in figs. 2 and 3. In some fields photographed collaterals outnumber surviving myelinated fibres by seven to one.

This extensive formation of compact and well-filled bundles of collaterals is most clearly seen where there are moderate numbers of normal fibres surviving. In those parts of the nerve trunk where severe deneurotization has occurred, and only a few myelinated fibres survive, many empty, or almost empty Schwann tubes are seen, with relatively few new sprouts invaginating around their periphery (figs. 4, 5 and 6).

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It is in this type of material that the funnel-like invagination, and the short attachment, already described in normal nerves, is most commonly encountered.

With increasing time the collaterals do not seem to mature markedly : their diameter increases slightly, but they seldom exceed 2 μ, myelination has not been observed. No material has been used from a post-operative period of more than twenty-one days, because of the chance of mistaking regenerating fibres from the proximal stump for collaterals.

No obvious difference in the amount of sprouting in the tibial nerve, and sciatic nerve in mid-thigh was noted : however, an entirely different picture was presented by the roots containing the intact fibres of these nerves (L4 and 6). No increase in non-myelinated fibres beyond the normal could be detected here, and it is assumed that no sprouting occurred at this level. It should be pointed out again that the numbers of non-myelinated fibres found in normal mixed limb nerves is such as to make difficult any systematic electron microscopic examination of them.

In some studies in collaboration with Professor G. Wohlfart,[1] numerous similarities have been demonstrated between the pattern of sprouting in traumatically affected nerves, and those of Theiler encephalytic mice. Figs. 7 and 8 illustrate the appearance of nerves from paralysed animals; fig. 7 resembles fig. 2, in that the region is a moderately denervated one, showing substantially reinnervated Schwann cells. Fig. 8, on the other hand represents portions of several large Schwann cells from substantially denervated regions. The central Schwann cell is reinnervated only along its inner edge, and numerous incompletely invaginated fibres may be seen.

For purposes of comparison, a few sections of partially denervated muscles (toe flexors), were examined. In the small intramuscular nerve bundles, as was expected, the collaterals were found to be much larger than those described above in the nerve trunk. After three or four days they were 2–3 μ in diameter, and the axoplasm was densely granular. Only one collateral was found in each Schwann cell.

It was felt that at least some of the new fibres found in the large nerve trunks ought to be demonstrable by classical histological means—after they had reached a diameter of perhaps 0·5 μ. Accordingly a study was made of nerves taken fourteen and twenty-one days after operation, stained, by Holmes (1947) method. Figs. 9 and 10 are taken from the

[1]Neurology Department, University Hospital, Lund, Sweden.

fourteen-day material. As may be seen in fig. 10, a few myelinated fibres survive, interspersed by columns of hypertrophied Schwann cells. In the less severely denervated regions, as described above, bundles of tiny fibres, occasionally traceable as branches of surviving myelinated fibres, have invaded the Schwann columns. In more severely denervated zones, only occasionally have the Schwann columns been invaded, but examples of this may be seen in figs. 9 and 10. Since these fibres are close to the minimum diameter demonstrable by the light microscope, it is probable that each Schwann column encloses more fibres than can be seen in these photographs.

The animals treated with pyronin did not differ from the rest, new sprouts were numerous and early in both groups. A quantitative analysis has not been made.

Discussion

That we are dealing here with the formation of a large number of new nerve-fibre branches, many of which never reach microscopic dimensions, seems clear. As has been demonstrated, the spaces between surviving myelinated fibres become closely packed with bundles of these fibres, resulting in the myelinated fibres being substantially outnumbered. The invasion of deneurotized Schwann cells by only a few collaterals at first, presents an appearance in marked contrast to the Schwann cells closely packed with non-myelinated fibres found in normal nerves. Collateral origin of these fibres is supported by their detection even twenty-four hours after operation, so far down the peripheral nerve. More direct evidence is available in a few cases from silvered sections.

The small diameter of these new branches, and their failure to mature, calls for comment. As has been pointed out earlier, collaterals formed within intramuscular nerve trunks mature much more rapidly, and only one collateral is found within each Schwann cell. The collaterals of the nerve trunk mature less than do regenerating fibres entering the distal stump of a severed nerve. Their failure to mature, and the persistence of numerous collaterals in each Schwann cell, may be due to inability to form terminal connexions, in accord with the results of Weiss, Edds and Cavanaugh (1945), and Aitken, Sharman and Young (1947).

A proportion of the collaterals undoubtedly reneurotize the Schwann cells of degenerated fibres—but many are enclosed within cells of smaller diameter, which show no evidence of debris absorption. Possibly these are derived from daughter Schwann cells which have resulted from mitosis. The rapidity with which the fibres are enclosed by Schwann cells calls for comment: it would appear that in these circumstances

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the collateral makes immediate contact with a Schwann cell. Naked axons have never been seen in this study.

The previous suggestion that a gradient of responsiveness exists along the motor axon, decreasing disto-proximally (Hoffman 1950) finds no support here. Examination of different portions of the sciatic nerve indicates no significant difference in the numbers of new fibres. The absence of sprouting within the undamaged segmental nerve roots supports the contention that only where close intermingling of degenerated and intact fibres occurs does sprouting result.

The fact that similar sprouting occurs when portions of the motor fibres in a mixed nerve degenerate as a result of Theiler virus infection is of some significance in this study. Degeneration will occur in both motor and sensory fibres when a lumbar segmental nerve is cut; therefore it is impossible to say whether the sprouts observed in these circumstances are from surviving motor or sensory fibres. However, Theiler encephalitis is strictly homologous with poliomyelitis, in that only anterior horn cells and their somatic motor fibres are affected, and only the motor fibres sprout within the muscle. It is therefore reasonable to suggest that the sprouting observed in these circumstances is of surviving motor fibres, into Schwann cells of degenerated ones.

It therefore appears that a phenomenon thought to occur only in the peripheral portion of the nerve fibre results wherever the stimulus is presented—wherever degenerated and intact nerve fibres are intermingled. It is probable that any portion of the neurone can sprout if presented with the appropriate stimulus. The axon appears to begin sprouting within a very short period of the interruption of nearby ones; the branches are at first submicroscopic, and depending on environmental conditions they may reach microscopic dimensions and undergo maturation and myelination. In some circumstances they may persist immature for long periods.

These results emphasize the significance, in nerve growth, of the non-terminal (collateral) mode of branching, and indicate that it plays a major part in the response of the nervous tissue to trauma. The special significance of the sprouting, following paralysis in Theiler virus-infected mice, in the interpretation of poliomyelitis is further assessed in a forthcoming paper (Wohlfart and Hoffman, in press).

Summary

An electron microscopic study has been made of the appearance of collateral nerve fibres in partially deneurotized nerves.

Large numbers of small (0·1 μ upwards) nerve fibres appear in such

nerves from twenty-four hours after operation onwards, invading deneurotized Schwann cell columns.

Little change occurs in their appearance during the first three weeks.

We wish to thank Mr. S. A. Edwards and Miss Joyce Dobson for their technical assistance, and the British Empire Cancer Campaign for financial support.

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LEGENDS TO PLATES

PLATE LXI

FIG. 1.—A group of nerve fibres in the vagus nerve: portions of four myelinated fibres are seen, as well as two bundles of non-myelinated fibres (*a*) and one individual fibre, all enclosed by Schwann membranes (*s*) within Schwann protoplasm (*s.p.*). In several places the mesaxons—attachments of axons to Schwann membranes—(*m*) may be seen.

FIG. 2.—A low-power electron micrograph of a rat tibial nerve, three days after section of L5. The region is one of slight denervation, and between the surviving myelinated fibres, numerous small, well-filled bundles of non-myelinated fibres may be seen, enclosed within Schwann cells.

FIG. 3.—Portion of tibial nerve of rat, twenty-four hours after L5 section. A single myelinated fibre is seen in the centre left, surrounded by packed non-myelinated collaterals.

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PLATE LXII

FIG. 4.—A fairly heavily denervated region of rat tibial nerve, four days after L5 section, treated with pyronin. Above the single myelinated fibre in the lower right, three Schwann cells are being invaded by collaterals (*c*). One collateral has only partially invaginated the Schwann membrane at (*f*) forming the characteristic funnel-shaped invagination. Within the invaginated fibre a single dense mitochondrion may be seen.

FIG. 5.—A substantially reinnervated Schwann cell from a tibial nerve two days after L5 section. Some of the collaterals are completely enclosed by the Schwann membrane, but two at (*f*) are still incompletely invaginated.

FIG. 6.—A severely denervated zone in tibial nerve three days after L5 section. Pyronin treatment. Apart from the single myelinated fibre in the top right, the field is occupied by four Schwann cells partly reneurotized by collaterals (*c*). The membrane of one Schwann cell is indicated (*s*). The central Schwann cell has been invaded by only one collateral.

FIG. 7.—Sciatic nerve of mouse, seventeen days after onset of paralysis due to Theiler virus. In amongst the myelinated fibres may be seen bundles of non-myelinated collaterals (*c*). This is from a moderately denervated zone, comparable with fig. 2.

PLATE LXIII

FIG. 8.—Portion of a more severely denervated mouse sciatic nerve, seven days after onset of Theiler-produced paralysis. Only one myelinated fibre is seen in the upper left, the rest of the field being occupied by partly reinnervated Schwann cells, their membranes being indicated by (*s*), the protoplasm by (*s.p.*). Some of the collaterals are incompletely invaginated, similarly to those in fig. 5, and funnel-shaped invaginations are shown at (*f*).

FIG. 9.—Longitudinal section of the tibial nerve of rat, fourteen days after L5 section, stained by Holmes silver method. One residual, myelinated fibre is seen (*r*), whilst the rest of the field is occupied mostly by columns of deneurotized Schwann cells. At (*c*) several fine collateral fibres are seen, passing along hypertrophied columns of Schwann cells. Portions of other, even finer, fibres may be seen elsewhere in the field.

FIG. 10.—From the same nerve as fig. 9. Portions of obliquely cut residual fibres are seen, but the field is substantially denervated. A small group of collaterals is seen at (c), accompanying enlarged Schwann cells.

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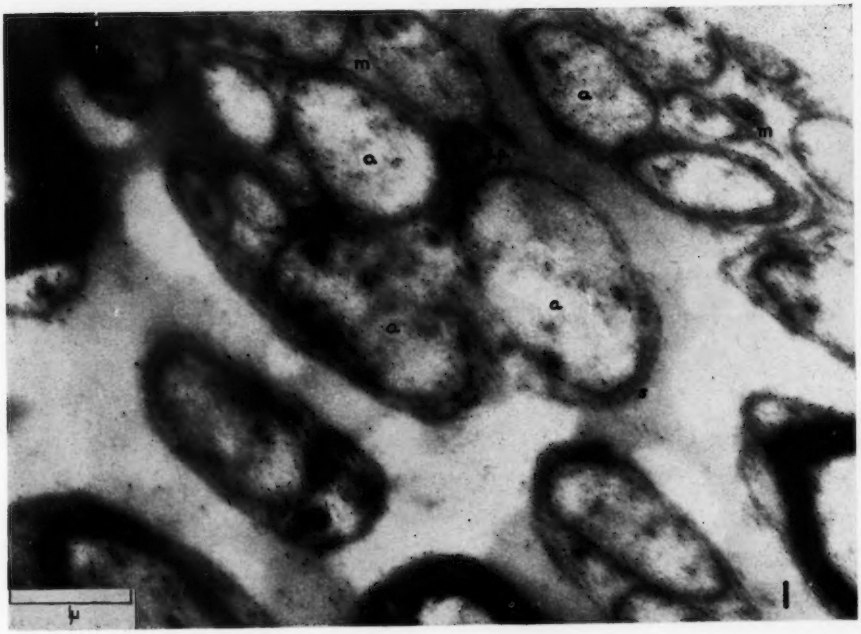
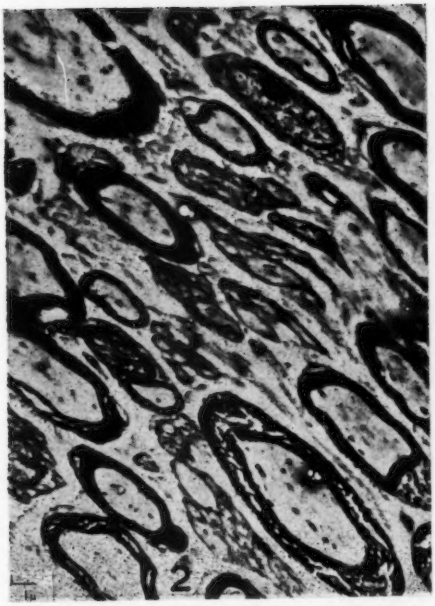
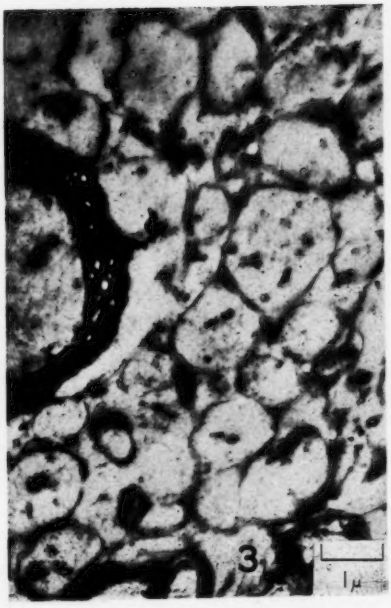
PLATE LXI







To illustrate article by G. Causey and H. Hoffman

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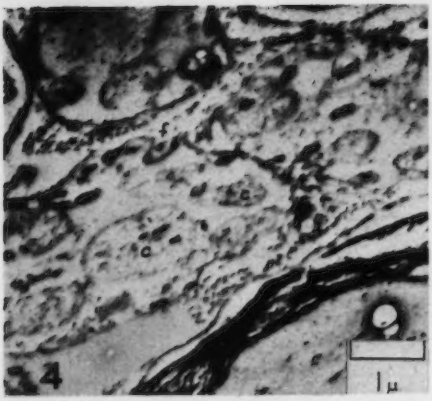

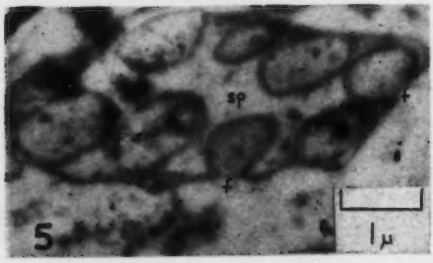

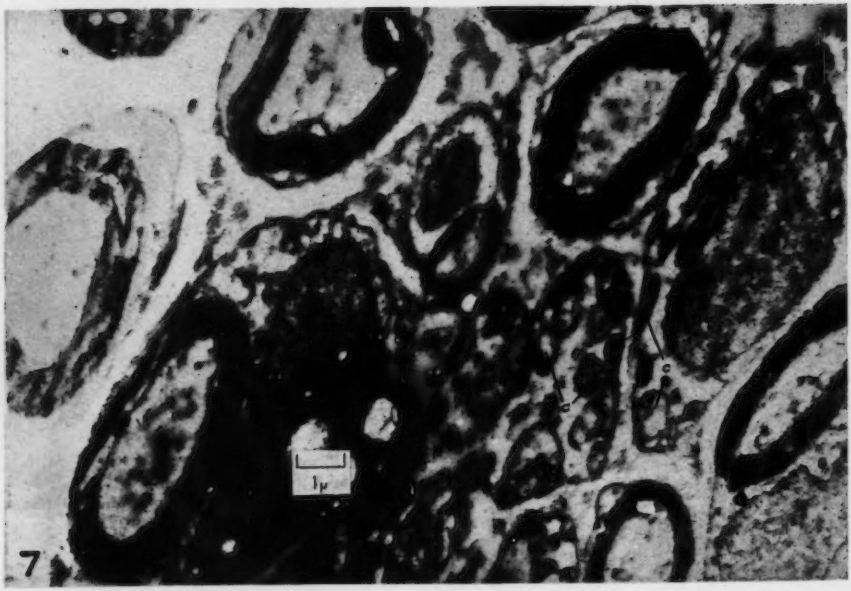

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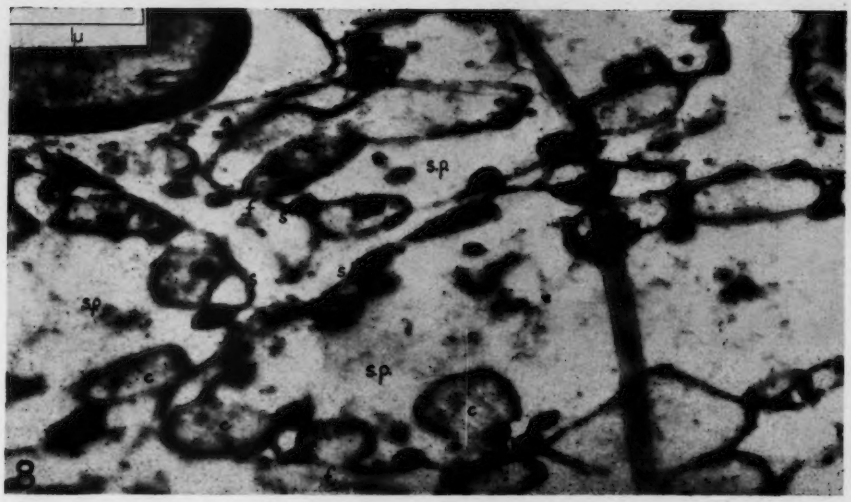

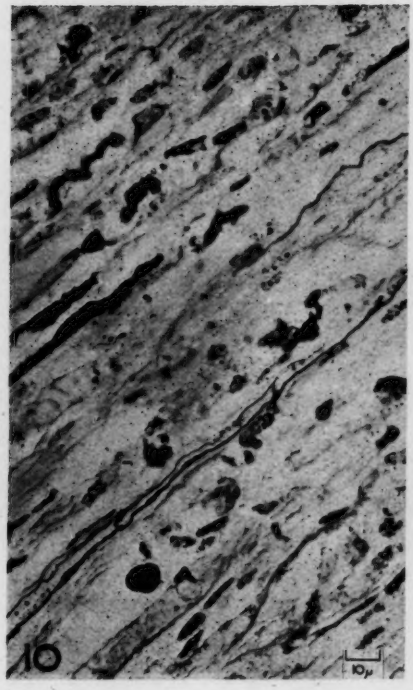

To illustrate article by G. Causey and H. Hoffman

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NOTICES OF RECENT PUBLICATIONS

MIND AND BODY

Brain Mechanisms and Consciousness: A Symposium. Ed. by J. F. DELAFRESNAYE. 1954. Pp. 556. Illustrated. Oxford: Blackwell Scientific Publications. Price 42s.

The relationship between brain mechanisms and consciousness is not purely a semantic question, but semantics play so large a part in it that no writer who fails to recognize this is likely to get very far. From the semantic standpoint this might be called a symposium upon a hyphen, the hyphen in the brain-mind relationship.

Broadly the first half of the book is concerned chiefly with anatomical and physiological description. Amongst others, Magoun writes on the ascending reticular system and wakefulness, Hess on the diencephalic sleep centres, Bremer on the neurophysiology of sleep and Brazier on the action of anæsthetics. The second half is devoted to more theoretical discussions of the facts of anatomy, physiology and psychopathology. Adrian writes on the physiological basis of perception, Gastaut on "cerebral electrogenesis," Penfield on the centrencephalic system, Grey Walter on theoretical properties of diffuse projection systems, and Jasper on the thalamic reticular system. Hebb, Lashley, and Kubie deal with the problem mainly from the psychological standpoint. Each paper is followed by a discussion, and a general discussion and a comprehensive bibliography end the book. The reader will find here some useful reviews, and much material for thought.

I have not so far mentioned the contribution which is central in the book and central also in its demonstration of the nature of the problem with which the book is concerned—Fessard's paper on "Mechanisms of Nervous Integration and Conscious Experience." Fessard distinguishes between mind and consciousness, and quotes with approval Cobb's statement that "it is the integration itself, the relationship of one functioning part to another, which is mind and which causes the phenomenon of consciousness." Fessard therefore defines consciousness as "experienced integration."

He then discusses what kind of neurophysiological mechanisms might be concerned in this process, especially in the central reticular system, though he has to confess that, if consciousness depends in this way upon patterns in space and time, "what makes a pattern 'conscious' of its own patterning remains an irritating problem." It does indeed, as the following selection from the views of contributors to this symposium shows. "Sensory information is integrated within the centrencephalic system" (Penfield). "I consider integration as a dynamic abstraction and not localizable in space" (Bremer); "If the diffuse system of projection plays a part in the regulation of cortical electrogenesis and the level of consciousness, these two factors are not directly dependent on each other and may evolve independently" (Gastaut). "The existence of something called consciousness is a venerable *hypothesis*: not a datum, not directly observable,

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but an inference from other facts . . . Consciousness is something within the head which determines behaviour, and which can be studied through that behaviour" (Hebb). "Although we cannot get along without the concept of consciousness, actually there is no such thing" (Kubie). "The knower as an entity is an unnecessary postulate" (Lashley).

If any result other than confusion is to emerge from a consideration of the difficult question of the brain-mind relationship it is necessary to be clear about three things. The first is the nature of cerebral localization or representation. It should by this time be more generally recognized that a function should not be said to be localized in some part of the brain merely because damage to that part interferes with it, or electrical stimulation there excites it into activity. Secondly, it is essential to recognize the distinction between the space of perception and the space of physics, and between perceptual objects and physical objects—a point stressed in recent years by a number of writers (Köhler, 1938; Russell, 1948; Hutton, 1950; Brain, 1951; and Smythies, 1954). It is especially important when speaking of the body or the brain to make clear whether it is the perceptual or the physical body or brain to which reference is being made. Finally a constructive discussion of consciousness requires a recognition of the logical relationship of the perceptual and physical worlds. Despite the wise caution of Adrian and Fessard many contributors to this Symposium seem to think that it should be possible to *explain* consciousness in psysiological terms, and are frustrated by the fact that this elusive fish always slips through the net. But, as Dingle (1952) says: "In any rational argument one must proceed from premises—from evidence—to conclusion, and not from conclusion to premises, and in the practical, common-sense philosophy it is the latter course that is taken. Experience is interpreted as a consquence of the action of the world of material objects on the sensitive body. But what we know immediately is experience; the world of material objects is what we (rightly or wrongly) infer from it, and a scheme which attributes the data to the action of an inference from the data thereby declares itself as essentially irrational. In the same breath we say there must be a world of matter because we have experiences, and we have experiences because there is a world of matter which causes them. On such a basis it is not to be expected that great systems of rational thought will be erected."

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RUSSELL BRAIN.

Mind and Body. By PEDRO L. ENTRALGO. 1955. Pp. 150. Harvill Press, London. Price 12s. 6d.

This modestly written book is subtitled "Psychosomatic Pathology: A Short History of the Evolution of Medical Thought." Professor Entralgo traces the development of human thought on the nature of disease from Assyro-Babylonian times down to the present day. He seeks to show that twentieth century psychosomatic pathology has derived much from primitive Christian thought. As

Professor Entralgo's use of the term "psychosomatic pathology" implies an anthropological approach, in the Thomian sense, to the problem of man in health and disease his conclusion is not surprising. This is a charming, well translated book, which is recommended to those who are interested in the philosophical aspects of medicine.

R. A. HENSON.

THE SURGERY OF PAIN

Pain: Its Mechanisms and Neurosurgical Control. By JAMES WHITE, M.D., F.A.C.S. and WILLIAM H. SWEET, M.D., F.A.C.S. 1955. Pp. 736, figs. 134. Charles C. Thomas, Springfield, Illinois. Price £6 6s. 0d.

The surgical treatment of intolerable pain is a subject in which interest will never wane, and in this book two experienced neurosurgeons make their contribution to its study. Part One of the volume is devoted to the fundamental aspects of the problem, the anatomy and physiology of pain conduction being fully discussed in a critical review of the literature, enlivened by observations made by the authors, who have been at pains, whenever opportunity offered without harm to the patient, to test the validity of theory by experiment. For example, after presenting the observations and conclusions of others upon the possibility of pain conduction in anterior nerve roots, with the weight of evidence against it, they record the effect of stimulation of the exposed roots in their own hands, in the course of thirty operations, showing that pain may be so produced under artificial conditions, but doubting whether this pathway is of any clinical significance. The balanced judgment thus expressed is characteristic of the authors' approach, and there are few aspects of the anatomy and conduction of pain upon which they have not something to say from their own experience. The discussion of visceral, and other deep-seated pains occupies a large part of this section, of which the final chapter is devoted to psychiatric considerations.

Part Two covers surgical technique, including diagnostic and therapeutic nerve block, peripheral neurectomy, posterior rhizotomy, cordotomy, tractotomy, leucotomy and sympathectomy. The diagrams in this section are admirably clear and well produced. The difficulties attending these procedures, and the complications and failures that may sometimes follow, are fully described, with particular reference to the authors' experience.

Part Three, dealing with specific painful conditions, will naturally excite the curiosity of the clinical reader wishing to sample the book, and whatever his particular interest, be it angina pectoris or phantom limb, he will be rewarded. The neurologist is likely to turn to the pages on trigeminal neuralgia and will find no flaw, except that there is no mention of the corneal reflex in the discussion of differential diagnosis from angle tumour. The authors' opinions as to the value of the different procedures for the relief of trigeminal neuralgia are closely reasoned, and their argument that alcohol injection of the ganglion be reserved exclusively for patients in whom surgical exposure is too hazardous a procedure is cogently presented. The discussion of glossopharyngeal neuralgia contains no reference to Deparis' excellent little monograph on this subject, nor is there mention of section of the nerve as it lies in the tonsillar bed, for which success has been claimed by others. Causalgia is well described and defined as a rare syndrome distinct from all other forms of pain following peripheral nerve lesions, with

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impressive figures for the value of sympathectomy. The atypical facial neuralgias are fully discussed with frank admission of surgical failures and ignorance of cause. These are but a few examples of the topics covered in this section, which is a mine of useful information presented in attractive style. The emphasis is naturally on treatment—its success or failure—and it is refreshing in a work of this kind to find so much of honest doubt emerging from clear thinking and hard-won experience.

The book for a number of reasons is easy to read. The print is large and clear, the data are so tabulated that reference is easy, the illustrations are apt and well charted, and all that it has to say is expressed in harmonious and lucid prose. This is a monograph worthy of the standards set by that great craftsman and scholar, Harvey Cushing, and by the two living neurosurgeons to whom the volume is dedicated.

C. P. SYMONDS.

INTRACRANIAL TUMOURS

THE SHERRINGTON LECTURES III. *The invasive adenomas of the anterior pituitary.* By Sir GEOFFREY JEFFERSON. 1955. Pp. 61. Figs. 25. University Press of Liverpool. Price 5s.

By his writings Sir Geoffrey Jefferson has been recognized as having a particular interest in lesions in the region of the sella turcica. Some fifteen years ago he made an outstanding contribution to the morbid anatomy of pituitary adenomas by his description of the extra-sellar extensions. The Sherrington Lecturer has now carried his studies farther, for here we have an account of those florid tumours which extend lateralwards rather than upwards. Out of a total of 312 cases of pituitary adenoma, 14 are described in which there had been spread of tumour into the cavernous sinuses. The ages of the patients varied from 19 to 65 years and in 4 there was acromegaly. The duration of life after the first symptom was as short as 3 months, and as long as 17 years. Analysis of the author's cases reveals that evidence of trigeminal nerve involvement provides strong indication of invasion of the cavernous sinus and if to this is added weakness of one or more of the ocular muscles the diagnosis is quite certain. In many cases all divisions of the gasserian ganglion were affected, and there was weakness of the masticatory muscles. Sir Geoffrey describes how the anatomy of the sella and the cavernous sinus may be so distorted by a massive adenoma as to render the ganglion and the motor root susceptible to damage. He emphasizes—as others have done—that third nerve palsy alone does not necessarily imply a cavernous sinus extension, for the nerve may be compressed at the point where it is entering the roof of the sinus by a mass arising out of the sella. This is an important detail, for such a palsy may improve after operation and is certainly no contra-indication to operation : whereas operation upon the type of adenoma dealt with in this paper is nearly always fatal. Irradiation is thought to be the better choice.

The adjective "invasive" is used to describe these adenomas, rather than "malignant" and whether they should be regarded as cancerous occupies the terminal section of the lecture. That they invade tissues is clear from their histology; and the morphology of the cells suggests that they have malignant characters. Metastases in the cerebrospinal fluid pathways have been reported, but there has been no reliable case of metastasis to organs elsewhere. The incidence of this type of adenoma is thought to be higher than the recorded cases imply, and Sir

Geoffrey suggests that perhaps it is as high as 1 in 10. The illustrations, particularly those of specimens, are excellent.

No one who has to deal with pituitary tumours can afford to miss the opportunity of reading this lecture. Those who are not particularly interested in this field, but who contemplate putting on record a series of cases illustrating a special aspect of the natural history of tumours could not do better than to study it, to see how it should be done.

Intracranial Gliomata. M.R.C. Special Report Series No. 254. By JOHN PENMAN, M.B., M.R.C.P. Neurologist, Hertford Co. Hospital, St. Andrew's Hospital, Bow and Haymeads Hospital; Clinical Assistant, St. George's Hospital, and Maida Vale Hospital: and MARION C. SMITH, M.B., B.Sc. On staff of M.R.C. Neurological Research Unit. 1954. Pp. 70. Tables 56. H.M. Stationery Office, London. Price 5s.

"This paper is a numerical enquiry into certain aspects of the intracranial gliomata, namely their main clinical features, their radiological signs and their responses to surgery and radiotherapy." The analysis deals with 298 cases, and the duration of the follow-up was a minimum of two years. In their opening sentence the authors use the word "numerical" and with this in view very detailed and extensive analyses are made of the many aspects from which this disease can be viewed. Their figures confirm the findings of other writers, that gliomas occur more commonly in the male, more commonly in the left hemisphere than in the right, and when correction is made for relative bulk more commonly in the temporal than in the other lobes. What the biological influences may be which determine these predilections remains a mystery. An attempt is made to assess the relative value of treatment by surgery and by irradiation, but the authors found this well-nigh impossible, and, to quote again, "the results of pure surgery were the best, but only because of much selection of favourable cases. Pure radiotherapy gave a fair proportion of good results, but their absolute number is so small that no reliable conclusion can be drawn." Very rightly, they stress the need for a controlled study of the effects of irradiation on intracranial gliomas, In assessing the value of treatment, the quality of survival is taken into account; 85 patients lived for more than twelve months, and in 52 the survival was considered useful. Their criteria are severe, and this makes for a gloomy picture. Nevertheless, one must set against this the unexpected long survivals, such as were emphasized by Eisenhardt in her review of Cushing's cases. Thus in the authors' series there were 13 patients with glioblastoma (out of a total of 149) who lived for three to ten years, and 21 with astrocytoma (out of a total of 70) who lived for from three to more than ten years, though in how many of the latter the lesion was cerebellar is not clear. Even though a patient may live less than a year after a palliative operation, it often happens that the period may be happy, and for part of the time without severe disability. Such experience, common to all neurosurgeons, makes their opinion, that change in the patient's condition lasting less than a year is "of little moment" perhaps somewhat harsh. "Of little moment" perhaps to the statistician, but by the patient and his relatives this short reprieve is usually most gratefully received.

DOUGLAS NORTHFIELD.

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RECENT ADVANCES

Recent Advances in Neurology and Neuropsychiatry. Sixth Edition, by SIR RUSSELL BRAIN, Bt., D.M., P.R.C.P., Physician, The London and Maida Vale Hospitals, and E. B. STRAUSS, D.M., F.R.C.P., Physician for Psychological Medicine, St. Bartholomew's Hospital. 1955. Pp. 311, figs. 46. Churchill, London. Price 30s.

Although the present volume is called the sixth edition, it is in fact a new work and is exactly described by its title. It begins topically enough with a statement of the present advancing knowledge of the special functions of those parts of the brain, the surgery of which is interesting the psychiatrist, contained in chapters on the frontal and temporal lobes. Then the senior author deals with integration of perception in the parietal lobes and with the present extraordinary advance in knowledge of the mechanisms serving the conscious state. After this general opening there are sections, as might be expected, on poliomyelitis, demyelinating disease and the neurological effects of vertebral disorder.

A short chapter on the cerebellum and its disorders has the advantage of Dr. Greenfield's and Professor Brodal's very recent statements on its pathology and anatomy.

There is a most inclusive chapter on electro-encephalography by Dr. Denis Hill which will serve as an adequate source of reference for any clinician who does not set up as an authority in this specialty, and which constitutes a particularly well-balanced statement of the relationship of electro-encephalography to clinical work. Dr. David Sutton has made a similar contribution in a chapter on radiology which is extravagantly illustrated by excellently produced negatives and line diagrams. Although much has been written about intracranial tumours in the past, a short chapter by Mr. Northfield brings the results of neurosurgery and radiotherapy up to date.

Those who, like the reviewer, have difficulty in keeping up with the literature will find in this volume an easy way of making up some lost ground.

DENIS WILLIAMS.

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A JOURNAL OF NEUROLOGY,

FOR

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